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ANAEMIA IN NEPHRITIS

BY

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The intractable anaemia of nephritis has been extensively investigated in adults, but there has been little detailed study of the blood changes occurring in the nephritis of childhood, though at this age period complicating factors are less common than in adults. It is generally agreed that the anaemia of nephritis is not markedly hypochromic; some indeed consider that it is orthochromic, and in some cases a colour index even above unity has been recorded. Furthermore, it has never been conclusively shown in which type of the disease the anaemia is most in evidence.

Parsons and Ekola-Strolberg (1933) state that anaemia is common in chronic nephritis, but after an extensive investigation of the literature and from their personal observations they conclude that anaemia is almost always present in cases with azotaemia regardless of the pathological basis of the renal insufficiency. They further claim that there is a parallel between the degree of anaemia and the extent of the azotaemia. They agree with van Slyke (1930) that anaemia is as valuable a prognostic sign as azotaemia. Grawitz (1911) believed that hydraemia produced an apparent anaemia, but he only found it to be present when cardiac decompensation developed. Thursfield (1934) observed that acute nephritis with oedema was often accompanied by a marked anaemia, but considered that this was more apparent than real as it was in all probability due to oedema of the blood.

Ceconi (1905) was the first to suggest that the anaemia was aplastic and due to toxic action on the bone marrow. This hypothesis is the one most widely held at the present time. Wintrobe (1934) drew attention to the similarity of the blood picture in the anaemias of nephritis, marrow aplasia, and the anaemia which he found in the various inflammatory diseases. All were normocytic or microcytic, but in none was there a marked hypochromia. In his series of cases of nephritis the average red cell count was 3·58 millions per c.mm., the average haemoglobin 70 per cent. (Haldane), and the average packed cell volume 30 per cent. Murphy et al. (1934) state that in acute nephritis a red cell count below 3·5 millions per c.mm. implies progressive breakdown of renal function.

The changes that oedema causes in the concentration of red cells have also been the subject of several investigations. As already noted, Grawitz (1911) believed that the anaemia of nephritis was simply the result of a hydraemic plethora secondary to cardiac decompensation. Reference has also been made to Thursfield's opinion that oedema of the blood occurs in many cases of acute haemorrhagic nephritis in which there is general oedema. McClure and his co-workers (1933) made a detailed study of the red cell count of capillary blood

in nephrotic oedema during its increasing, stationary and subsiding phases. They found that the red cell count, haemoglobin and packed cell volume all increased as the oedema advanced, decreased with stationary oedema and still further decreased when diuresis occurred and oedema lessened. They considered that these changes might be explained by movement of fluid from the blood to the tissues during the period of increasing oedema, whereas during lessening oedema fluid returned from the tissues to the blood and concluded that in the nephrotic syndrome the fault lies in the tissues rather than in failure of the kidneys to excrete water. Such an explanation cannot be considered conclusive without further facts being known, as it does not take into consideration the possibility that the increasing cell counts may be due partly to the expulsion of red cells from the blood depots of the body into the circulating blood as well as to subtraction of fluid from it.

Thus a survey of the literature shows that, whilst most workers agree that anaemia frequently occurs in nephritis, there is considerable difference of opinion regarding the type of nephritis in which anaemia is found, and the character of the anaemia when it does occur. In the present investigation an attempt has been made to gather fresh information on these two points.

Method of investigation

Duplicate red cell counts, using separate pipettes for each, were done at intervals of not more than a week on all cases. If the difference between the two counts was not more than 200,000 per c.mm. the average was taken to express the true count, but if the difference was greater than this, the results were discarded and the process repeated. Capillary blood was obtained by puncturing the lobe of the ear with a Hagedorn needle and venous blood was aspirated from a vein in the ante-cubital area with minimal venous stasis. Haemoglobin was estimated by Haldane's method at the same time as the red cell counts were made. White cell counts were done weekly and the average of duplicate counts was taken. At the first examination of each case, reticulocyte counts were made from preparations stained with brilliant cresyl blue, and these were repeated as circumstances suggested. At the same time films were stained with Leishman's stain and examined for abnormal cells. Serum protein was estimated by the dipping refractometer. The urinary volume and the patient's weight were measured daily. The degree of oedema was noted at the time of each count.

The packed cell volume was estimated by the haematocrit at intervals of approximately two weeks. About 6 c.c. of blood was withdrawn from an elbow vein with minimal venous stasis into a 10 c.c. haematocrit tube containing 2 c.c. neutral potassium oxalate solution to prevent coagulation. The blood was covered with a thin layer of liquid paraffin to prevent evaporation and centrifugalized at 3000 revolutions per minute for 30 minutes. In the earlier tests a solution of 1·6 per cent. neutral potassium oxalate was employed to prevent coagulation as recommended by Hooper et al. (1920). Later, in view of the criticism by Graff and Clarke (1931) of this method a 1·1 per cent. solution of neutral potassium oxalate was employed with more satisfactory results. From the red cell counts and the haematocrit readings the mean corpuscular volume was calculated according to the formula of Wintrobe (1934).

The effect of oedema on the accuracy of counts on capillary blood. When withdrawing blood by skin puncture in oedematous patients it is possible that there may be dilution of the blood by admixture with fluid from the oedematous

tissues. In order to decide whether this was sufficient to invalidate counts made on capillary blood a series of red cell counts and haemoglobin estimations was done on blood obtained by skin puncture and on blood withdrawn from a vein. The venous blood was mixed with a little powdered oxalate in a glass tube and then carefully but thoroughly mixed immediately before the estimations were made. Eighty-three of these duplicate blood counts, capillary and venous, were done on thirteen subjects. Thirty-nine of the counts were done at a time when there was no oedema, as shown by the absence of pitting on pressure and puffiness of the face and by a stationary weight. Forty-four were done during a phase of oedema which varied in degree from simple pitting on pressure over the shins to gross anasarca. The results are summarized in table 1.

TABLE 1

AVERAGES OBTAINED OF EIGHTY-THREE DUPLICATED BLOOD COUNTS ON VENOUS AND CAPILLARY BLOOD IN OEDEMATOUS AND IN NON-OEDEMATOUS INDIVIDUALS

OEDEMATOUS GROUP (44 COUNTS)		NON-OEDEMATOUS GROUP (39 COUNTS)	
CAPILLARY BLOOD R.B.C. PER C.MM.	VENOUS BLOOD R.B.C. PER C.MM.	CAPILLARY BLOOD R.B.C. PER C.MM.	VENOUS BLOOD R.B.C. PER C.MM.
4,164,000	4,105,000	3,991,000	3,832,000
Mean difference 59,000		Mean difference 159,000	
Standard error .. .. .. ±38,000		Standard error .. .. .. ±25,000	
Standard deviation 254,000		Standard deviation 155,000	

Standard error of the difference between the mean differences: 46,000

In the non-oedematous group the capillary blood is 159,000 (±25,000) red blood cells per c.mm. more concentrated than the venous blood. If excessive tissue fluid produces dilution of capillary blood during its collection then the increased red cell concentration of the capillary blood in the oedematous group should be less than 159,000 per c.mm. The figures in table 1 reveal that the mean difference between the averages in the oedematous group is indeed less than 159,000, namely, 59,000 (±38,000) red blood cells per c.mm. That is to say, the presence of oedema has, on the average, produced a false dilution of 100,000 red blood cells per c.mm. and it remains to calculate whether such a figure is statistically significant. To be significant the diminution in concentration of capillary blood should be more than twice the standard error of the difference between the mean differences which is 46,000. This proved to be the case in the present instance.

This difference in the counts in the two groups is capable of two explanations. The diminution in the relative concentration of the capillary blood in the oedematous group may be due to dilution of the blood flowing from the punctured lobe of the ear by excessive tissue fluid. On the other hand, the

extra congestion of the veins necessary to secure a sample of venous blood in an oedematous subject may produce some concentration of the blood in the veins.

It is impossible to state which of these processes is predominant and, almost certainly, both contribute something to the result. If the first suggestion is correct it would be preferable to do all blood counts on venous blood when studying anaemia in nephritis. But the accuracy of individual counts must also be considered since it is with individual counts, during oedema and after it has subsided, that the observations on the degree of anaemia of a patient will be judged subsequently. Examination of the individual counts shows that the venous counts on any one subject have a much wider week-to-week variation than have the capillary counts. This is shown in table 1 where the standard deviation of the differences in the oedematous group (254,000) is considerably larger than that in the non-oedematous group (155,000).

From these results it appears that in the presence of oedema blood counts made either from capillary or venous blood are subject to error. In the former there is some degree of dilution, in the latter of concentration. In neither case, however, is the error great, and in view of the fact that capillary blood is much more easily withdrawn than venous, all counts have been made from blood obtained by skin puncture. It must, however, be borne in mind that in capillary blood oedema may produce a false lowering of the red cell count by about 100,000 red blood cells per c.mm. and a proportionate reduction in haemoglobin and other blood constituents.

The material investigated and the results obtained

Thirty-six cases of nephritis were studied by the methods detailed above. They fall into the following four classes.

(1) Acute haemorrhagic nephritis—21 cases.
(2) The nephrotic syndrome (Volhard and Fahr)—5 cases.
(3) Nephrosclerosis—5 cases.
(4) Chronic haemorrhagic nephritis—5 cases.

Acute haemorrhagic nephritis. (Tables 2 and 3). All the patients in this group showed the typical signs and symptoms of the disease. Their illness was characterized by sudden onset, often after a streptococcal infection, with constitutional symptoms such as headache, vomiting, anorexia and pain in the back; with two exceptions all of them gave a history of oedema at the onset of the disease and sixteen were oedematous on admission. All had albuminuria, haematuria and hyaline, granular and blood casts in the urine; the blood pressure was above normal in all but three cases. In about half of the cases the non-protein nitrogen was above 40 mgm. per cent. at the first examination. All except one of the cases were well and had a normal urine within three months of the onset of the disease. In the single exception nearly seven months elapsed before the urine was free of albumin.

In table 2 the results of the blood examinations made during the acute stage of the disease are shown. From this it will be seen that there is a moderate

degree of anaemia and a colour index of 0·9. The mean packed cell volume of 36·7 per cent. is reduced below the normal of 46·6 per cent. in almost exactly the same proportion as the reduction in the red cell count, and gives a normal mean corpuscular volume of 86 cubic microns.

TABLE 2

THE BLOOD IN ACUTE NEPHRITIS EARLY IN THE DISEASE AND DURING CONVALESCENCE

SOON AFTER ADMISSION TO HOSPITAL					6 TO 8 WEEKS AFTER ADMISSION TO HOSPITAL				
NAME	RED CELLS PER C.MM.	Hb. PER CENT. (HALDANE)	WHITE CELLS PER C.MM.	R.B.C. VOL. PER CENT.	NAME	RED CELLS PER C.MM.	Hb. PER CENT. (HALDANE)	WHITE CELLS PER C.MM.	R.B.C. VOL. PER CENT.
D. F. ..	4,033,500	80	11,400	40·6	E. R. ..	4,560,000	80	11,100	—
A. J. ..	4,025,000	72	13,200	35·0	W. S. ..	4,645,000	93	11,000	—
E. R. ..	4,755,000	74	12,700	—	M. E. ..	4,540,000	86	8,300	—
W. S. ..	4,205,000	84	22,900	40·4	E. McI.	4,785,000	90	11,300	46·5
M. E. ..	4,735,000	92	7,200	42·9	G. H. ..	3,750,000	78	11,700	36·1
E. McI.	4,965,000	90	13,300	46·6	G. C. ..	4,440,000	90	7,100	44·6
I. M. ..	4,235,000	72	15,200	39·6	F. C. ..	5,210,000	90	8,600	—
R. M. ..	3,985,000	70	12,500	35·8	E. M. ..	4,135,000	70	9,000	37·8
G. H. ..	4,520,000	92	11,900	43·5	F. G. ..	4,525,000	78	8,400	37·2
H. G. ..	3,730,000	70	18,500	38·4	A. R. ..	3,520,000	72	8,900	30·0
M. W. ..	3,730,000	72	7,300	39·1	D. T. ..	4,410,000	86	5,800	38·0
G. G. ..	3,660,000	72	14,800	33·8	W. H. ..	3,800,000	72	8,000	35·0
F. C. ..	4,265,000	74	14,200	37·1	M. S. ..	4,050,000	83	4,900	40·5
E. M. ..	4,610,000	78	26,200	39·0					
E. S. ..	4,930,000	88	16,300	43·0	Averages	4,340,000	82	8,800	38·4
M. M. ..	3,985,000	78	13,900	38·8					
F. G. ..	4,715,000	80	11,600	38·5					
A. R. ..	3,665,000	70	11,000	34·0					
D. T. ..	4,785,000	88	8,200	39·0					
W. H. ..	3,585,000	72	15,000	30·0					
M. S. ..	4,650,000	82	9,800	35·0					
Averages	4,289,000	77	13,700	36·7					

Averages of above group on admission (extracted from first table)

4,390,000	79·8	13,800

Average colour index 0·9.
Average individual red cells volume, 86 cubic microns.
Eight of the patients in the first table are omitted from the second table. They had been dismissed home before six weeks had elapsed.

Thus, on the first examination the patients in this group presented a slight normocytic anaemia with a colour index of 0·9, a blood picture which, according to Parsons and Ekola-Strolberg (1933), may be considered to be orthochromic; there was also a moderate leucocytosis. As these counts only showed the state of the blood in the early stages of the disease the possibility had to be considered that anaemia had not then occurred, and that estimations made some time later might disclose its subsequent development. Of the twenty-one patients in this group eight were dismissed from hospital within six weeks of the first counts being made. In the remaining thirteen patients the results of the blood examination, made six to eight weeks later, are given in table 2.

This shows that there has been no increase in the anaemia, but that the leucocytosis has disappeared.

It would appear from these results that early in acute nephritis there is a slight orthochromic, normocytic anaemia with slight leucocytosis and that when convalescence is established the anaemia persists though there is no longer leucocytosis. During the course of the illness, however, definite changes in the blood picture were observed in all cases in which there was oedema. In table 3 the red cell counts are shown at three stages of the disease: (1) when

TABLE 3

RED CELL COUNTS IN DIFFERENT PHASES OF ACUTE NEPHRITIS

NO.	NAME	RED CELLS PER C.MM.		
		OEDEMA + OR + +	FIRST RECORD WHEN NO OEDEMA DIURESIS + +	4 TO 5 WEEKS LATER NO OEDEMA NO DIURESIS
1	D. F.	4,335,000	5,160,000	Irreg. Dismissal
2	A. J.	4,025,000	5,130,000	4,010,000
3	E. R.	4,755,000	5,115,000	4,440,000
4	W. S.	4,205,000	4,635,000	4,325,000
5	R. M.	3,985,000	4,375,000	—
6	M. W.	3,730,000	4,065,000	—
7	G. C.	3,660,000	4,315,000	4,000,000
8	F. C.	4,265,000	5,455,000	4,770,000
9	M. M.	3,985,000	4,640,000	4,045,000
10	A. R.	3,665,000	4,210,000	3,825,000
11	D. T.	4,785,000	5,020,000	4,410,000
12	W. H.	3,585,000	4,340,000	3,655,000
Averages *		4,103,000	4,762,000	4,164,000

(* Excluding no. 1, 5 and 6.)

oedema was manifest; (2) immediately after all clinical oedema had disappeared —the time when diuresis was most marked; (3) four weeks later when the weight was steady and the vascular water exchange was balanced. Only twelve of the twenty-one cases in this group are included, as the other children, when first examined, either had no oedema or were already in the stage when diuresis had begun. It will be seen that there was a pronounced rise in the red cell count during the period of diuresis and that the red cell count returned to its original level when oedema had disappeared and diuresis had ceased. This is illustrated in chart I, which shows the changes in the blood of W. H., a typical case of acute nephritis with oedema; similar changes occurred in all the other cases.

The nephrotic syndrome (tables 4 and 5). Although it is generally recognized that anaemia is not a feature of nephrosis there is difficulty in estimating the true state of the blood as there are variations in the blood count according to the stage of the disease at which the examination is made. In table 4 the red cell count, the haemoglobin percentage, the white cell count and the red cell volume in five children showing the nephrotic syndrome are given. These

CHART I.

Chart to Show the Relationship Between the Red Cell Count, Degree of Oedema and Urinary Excretion in Acute Nephritis.

W.H. 7 years. Acute Nephritis.

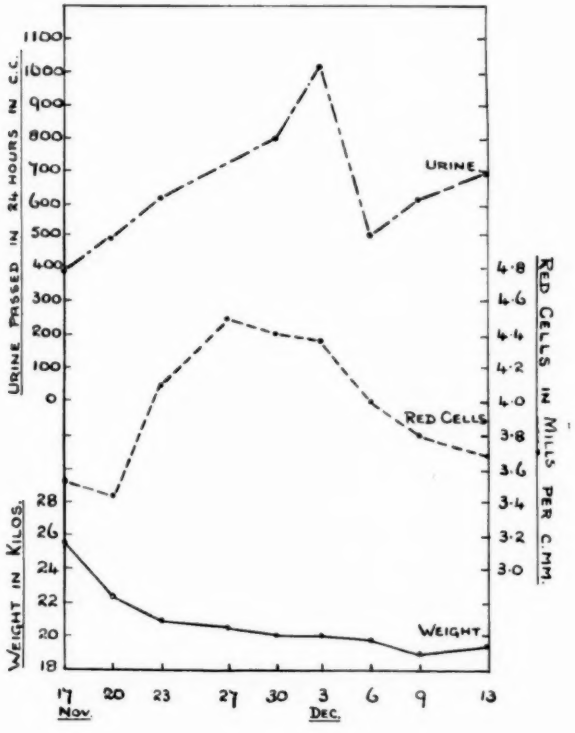


TABLE 4

THE BLOOD IN THE NEPHROTIC SYNDROME

NAME	RED CELLS PER C.MM.	Hb. PER CENT. (HALDANE)	WHITE CELLS PER C.MM.	R.B.C. VOL. PER CENT.	RETICULO-CYTES PER CENT. OF R.B.C.
T. M.	5,640,000	103	6,400	55·1	0·9
J. M.	5,495,000	104	13,400	47·0	0·6
W. G.	4,090,000	78	23,500	39·0	1·2
I. D.	3,810,000	66	17,300	32·4	—
E. G.	4,055,000	78	13,900	33·0	1·4
Averages ..	4,608,000	86	14,900	41·3	1·02

Average colour index 0·93.
Average mean corpuscular volume 90 c. microns.

figures represent the state of the blood on admission to hospital. They do not, however, necessarily show whether true anaemia is present or not as the

possibility that the fluid constituents of the blood may have passed out of the circulation into the tissues and led to haemoconcentration must be taken into consideration, nor can the possible influence of infections be overlooked. A brief summary of the course of the disease in each patient during his stay in hospital affords evidence of the part played by disturbance of fluid distribution and of the influence of infections as a cause of anaemia in this disease.

TABLE 5

NEPHROTIC SYNDROME

BLOOD AND URINARY FINDINGS DURING PERIODS OF INCREASING AND DIMINISHING OEDEMA

NAME	OEDEMA	Hb PER CENT.	R.B.C. PER C.MM.	CELL VOL. PER CENT.	URINE C.C. 24 HR.	N.P.N. MGM. PER CENT.	BLOOD Cl MGM. PER CENT.
J. M.	Increasing	104	5,495,000	47·0	480	32·4	443
	Diminishing	96	4,910,000	40·0	570	22·7	472
W. G. . .	Increasing	95	4,815,000	46·3	660	24·9	410
	Diminishing	82	4,110,000	40·0	640	19·0	484
T. M.	Increasing	103	5,640,000	55·1	230	35·7	432
	*Diminishing	68	3,670,000	36·2	1350	25·9	443

* The low results for T. M. when oedema was diminishing were due to the super-added effect of infection.

T. M. Admitted 20.7.38. Age 6 years 11 months. During his first three years the boy had frequent minor chest complaints, but thereafter remained healthy until two days before admission, when his face became puffy and on the following day he had swelling of his face, abdomen, scrotum, back and legs.

On admission he had anasarca and ascites with oliguria, albuminuria (28 parts Esbach), casts and scanty red cells in the urine. Blood pressure 122/92 mm. Hg. The Mantoux tuberculin test was negative. Temperature, pulse and respirations were normal. Oedema at this time was increasing. The blood examination gave the following results:

RED BLOOD CELLS	5,640,000 per c.mm.
HAEMOGLOBIN	103 per cent.
WHITE BLOOD CELLS	6400 per c.mm.
RETICULOCYTES	0·9 per cent.
RED BLOOD CELL VOLUME	55·1 per cent.
SERUM PROTEIN	5·13 gm. per cent.
NON-PROTEIN NITROGEN	35·7 mgm. per cent.

After one week he developed an erysipelatous rash followed by an empyema and in the course of four weeks his blood picture changed greatly.

RED BLOOD CELLS	3,160,000 per c.mm.
HAEMOGLOBIN	52 per cent.
WHITE BLOOD CELLS	23,400 per c.mm.
RETICULOCYTES	2·6 per cent.
RED BLOOD CELL VOLUME	35·9 per cent.
SERUM PROTEIN	5·25 gm. per cent.
NON-PROTEIN NITROGEN	35·2 mgm. per cent.

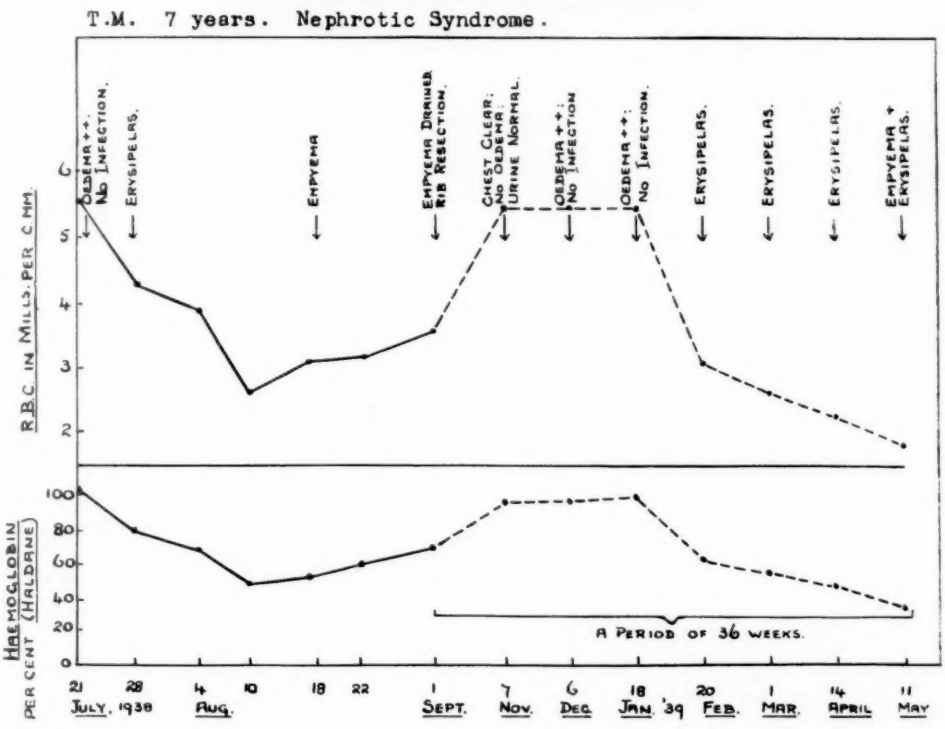
The blood pressure was 134/100 mm. Hg. The empyema was treated by rib resection and he was dismissed from hospital on 19.11.38 apparently well. There was no oedema, the blood pressure was 108/80 mm. Hg, the urine was free from albumin and blood and the following figures show that his blood had become normal.

RED BLOOD CELLS	5,225,000 per c.mm.
HAEMOGLOBIN	96 per cent.
WHITE BLOOD CELLS	8,600 per c.mm.
RETICULOCYTES	0·9 per cent.
RED BLOOD CELL VOLUME	47·0 per cent.
SERUM PROTEIN	7·32 gm. per cent.
NON-PROTEIN NITROGEN	41·7 mgm. per cent.

He remained well, at home, for two weeks and was then re-admitted to hospital with clinical, biochemical and haematological findings as on his first admission. Anasarca and ascites became extreme and his abdomen was tapped several times. After approximately six months of varying degrees of oedema he again developed erysipelas and pneumonia complicated by empyema. Associated with this there were severe anaemia and well sustained leucocytosis reaching 46,400 white blood cells per c.mm. (chart II). He died as a result of the pulmonary infection. In this last infection his blood count fell as low as 1,825,000 red blood cells per c.mm. and haemoglobin to 36 per cent., while the reticulocyte count varied between 5 per cent. and 10 per cent.

CHART II

Chart to show the Relationship between the Incidence of Anaemia and Infection in Nephrotic Syndrome.



The post-mortem examination revealed a left-sided empyema with a collection of pus under the diaphragm and bilateral pneumonic consolidation. The kidneys presented the typical characteristics found in lipoid nephrosis.

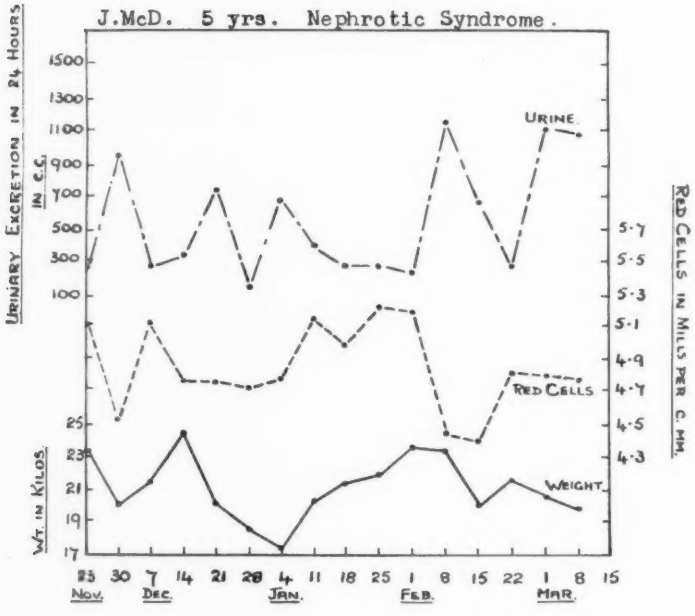
J. McD. Admitted 7.7.36. Aged 3 years 10 months. The boy had a normal, healthy childhood until two weeks before admission when his face became puffy and oedema rapidly spread over his whole body.

On admission there was anasarca and ascites with oliguria. The urine contained much albumin and many casts, but only scanty red cells. The Mantoux test was negative, the blood pressure 110/59 mm. Hg, the blood urea 28 mgm. per cent. and the serum protein 4·9 gm. per cent.

Since then he spent most of his life in hospital with waxing and waning oedema, but no impairment of renal function as shown by the urea clearance tests. During one week when he had a sudden increase in oedema his blood count was red blood cells 6,185,000 per c.mm., haemoglobin 126 per cent., and a week later when oedema was diminishing the count fell to red blood cells 4,790,000 per c.mm., haemoglobin 98 per cent. The boy repeatedly showed fluctuations in his red cell count associated with oedema similar to the example quoted, though less extreme. Although he was seldom oedema free, his general health remained fairly good until May and June, 1939, when he had several brief attacks of cellulitis of his thighs and abdominal wall with associated constitutional upset. On each of these occasions there was a sudden fall in the red cell count. Ultimately on June 23, 1939, he developed cellulitis of his legs, thighs and abdominal wall which led to generalized pneumococcal peritonitis and death exactly three years after the onset of his illness. In the

CHART III

Graph to Show the Relationship Between Red Cell Count, Degree of Oedema and Urinary Secretion in the Nephrotic Syndrome.



course of this fatal infection he developed severe anaemia. Blood examination gave the following results:

Red blood cells	2,785,000 per c.mm.
Haemoglobin	48 per cent.
Colour index	0·9.
White blood cells	27,300 per c.mm.
Reticulocytes	4·0 per cent.

The non-protein nitrogen was 34·2 mgm. per cent. and the serum protein 5·73 gm. per cent. His urinary output became scanty, contained albumin and occasionally a few red blood cells, and the chloride content was low. The blood pressure was 98/78 mm. Hg.

On post-mortem examination he was found to have a generalized pneumococcal peritonitis; no lung lesion; the heart and blood vessels were normal and both kidneys presented the characteristic picture of nephrosis.

W. G. Admitted 27.12.37. Aged 6 years. The boy had bone tuberculosis at four years. In December, 1936, he spent five months in another hospital with nephritis and oedema. After being at home for one month he was admitted to still another hospital where he remained for five months with nephritis and oedema. He was at home again for one month and then was admitted to this hospital with widespread oedema and ascites, gross albuminuria and many casts, but no red cells in his urine. The Mantoux test was positive.

On admission the blood findings were as follows:

Red blood cells	4,090,000 c.mm.
Haemoglobin	78 per cent.
White blood cells	23,500 per c.mm.
Reticulocytes	1·2 per cent.
Red blood cell volume	39·0 per cent.
Serum protein	4·57 gm. per cent.

The non-protein nitrogen was 27·8 mgm. per cent. and the blood pressure 106/70 mm. Hg. Oedema gradually disappeared and six months later, when he was transferred to a sanatorium with pulmonary and abdominal tuberculosis, his blood examination gave the following results.

Red blood cells	5,190,000 per c.mm.
Haemoglobin	94 per cent.
White blood cells	15,300 per c.mm.
Red blood cell volume	48·3 per cent.
Serum protein	5·96 gm. per cent.

Non-protein nitrogen was 38·6 mgm. per cent. and the blood pressure 94/66 mm. Hg. Throughout his stay in hospital his urine contained much albumin, but no red blood cells.

I. D. Admitted 13.7.37. Aged 4 years. The girl had a normal childhood. Three days before admission she became listless with anorexia and vomiting and her face was puffy. On the day of admission her legs and face became swollen and she had severe abdominal pain with nausea and vomiting.

On admission she had anasarca and ascites, fluid in both pleura and her urine contained much albumin, but only occasional red cells and casts. Both fundi were normal; the Wassermann reaction was negative and the blood pressure was 85/60 mm. Hg.

Oedema remained extreme until one month after admission when she

developed peritonitis from which she recovered after ten days. She was very fevered during this time and the serum protein rose to 6·47 gm. per cent. with some slight and temporary diminution in oedema. One month later an abscess pointed in the left iliac fossa, was aspirated and cleared up rapidly. Two weeks later the oedema increased and she was given 1 c.c. salyrgan intravenously; this was followed by rapid loss of all oedema. She remained without oedema or albuminuria for about three months. Then the oedema and albuminuria returned and failed to respond to further injections of salyrgan. Thereafter massive oedema was constantly present. During the latter half of November, 1937, she had a respiratory infection and in March, 1938, she developed generalized peritonitis and died. In her case the routine investigations described in this paper were only begun in February, 1938, five weeks before her death. The low blood counts recorded (table 4) for this girl are certainly attributable to the infections from which she suffered.

E. G. Admitted 2.11.37. Aged 3 years. The boy had a normal childhood until four days before admission when his face became puffy and the swelling rapidly spread over his body.

On admission he had generalized oedema and the urine showed a large amount of albumin and numerous casts, but no red cells. The Mantoux test was negative. The condition of his blood was as follows:

Red blood cells	4,055,000 per c.mm.
Haemoglobin	70 per cent.
White blood cells	13,900 per c.mm.
Reticulocytes	1·4 per cent.
Red blood cell volume	33·0 per cent.
Serum protein	5·61 gm. per cent.

The non-protein nitrogen was 23·9 mgm. per cent. and the systolic blood pressure 82 mm. Hg.

Ten days later he developed whooping cough and was transferred to a fever hospital. At that time his counts were:

Red blood cells	4,775,000 per c.mm.
Haemoglobin	86 per cent.
White blood cells	22,100 per c.mm.
Reticulocytes	1·1 per cent.
Red blood cell volume	42·0 per cent.

The non-protein nitrogen was 27 mgm. per cent. and the blood pressure 90/60 mm. Hg and oedema was diminishing.

It is worthy of note that in contrast to the effects of pyogenic infection observed in the previous case whooping cough did not cause increase in the anaemia in this child.

In order to get a true estimate of the state of the blood in a patient with nephrosis the count must be made when the child is losing oedema or, if possible, when he is oedema free. Only three of these patients (J. McD., W. G., T. M.) were observed over periods long enough to justify tabulation of the results. These are presented in table 5 in which the influence of oedema on various blood constituents is recorded. In this table it can be seen that there is a concentration of the blood during increasing oedema and a subsequent dilution during the phase of diminishing oedema. The increase in blood

chlorides during diminishing oedema is probably due to the transference of tissue fluid with a high chloride content to the blood stream during this phase.

Reference has already been made to the finding of McClure et al. (1933) that during the phase of increasing oedema in nephrosis the red cell count, haemoglobin, and the packed cell volume all increase and when the oedema becomes stationary or is subsiding and diuresis is profuse they fall. Each of the three cases was examined in detail over a sufficiently long period to show these changes. They are well illustrated in table 5 and by the case of J. McD. (chart III). This child was a typical example of the nephrotic syndrome and blood examinations were made on him at weekly intervals over a period of almost eight months as well as at other times. During that period of continuous examination he repeatedly showed the characteristic fluctuations in the blood constituents associated with the waxing and waning of oedema as described above.

One of these children (T. M.) had an acute infection on two occasions and on each a rapidly developing and severe anaemia was observed. On the first occasion the anaemia cleared up entirely after an empyema had been drained and had healed, but on the second occasion the boy died as a result of an empyema and erysipelas of his thighs (chart II). Another child in this group (J. McD.) also developed a severe anaemia associated with an acute infection from which he ultimately died.

The results in tables 4 and 5 and chart III afford further evidence in favour of the general opinion that anaemia is slight or absent in patients with nephrosis so long as they remain free from acute pyogenic infections. The high percentage of reticulocytes found during these acute anaemias indicates that the bone marrow is not rendered aplastic.

Nephrosclerosis and renal dwarfism (chronic interstitial nephritis) (tables 6 and 7). Of the five cases described here one was a renal dwarf and four were cases of chronic interstitial nephritis (nephrosclerosis).

TABLE 6

THE BLOOD IN CHRONIC INTERSTITIAL NEPHRITIS (NEPHROSCLEROSIS) SOON AFTER ADMISSION

NAME	RED CELLS PER C.MM.	Hb. PER CENT. (HALDANE)	WHITE CELLS PER C.MM.	R.B.C. VOL. PER CENT.
J. D.	4,260,000	74	10,800	40·2
M. McN. ..	5,415,000	108	7,800	44·7
J. C.	4,375,000	86	11,700	43·8
R. M.	2,460,000	50	11,200	24·3
E. D.	5,330,000	99	—	41·0
Average ..	4,368,000	83	10,400	38·8

Colour index 1·0.
Average volume of individual red cells 89 c. microns.

The renal dwarf (J. D.) was a boy aged 9 years who was first admitted to hospital in 1936 with double hydronephrosis and chronic pyuria. There was

thirst, polyuria and fatigue and failure to grow. He was re-admitted with the same symptoms in November, 1938. His systolic blood pressure was 72 mm. Hg and his urine contained albumin, numerous pus cells and streptococci, but no red blood cells. Skiagrams of his wrists showed signs of rickets. Both fundi were normal. The non-protein nitrogen was 83·3 mgm. per cent. and the serum protein 7·35 gm. per cent. Three of the other four cases (M. McN., J. C., E. D.) were all advanced examples of nephrosclerosis. In each the onset was insidious with headache and vomiting as prominent features and none of them gave any history of an acute attack of nephritis. They never had any oedema and not more than one or two red cells were ever found in their urine during the time they were in hospital. The systolic blood pressure was over 200 mm. Hg in each case and there was mild albuminuria. All had azotaemia and well-marked neuro-retinitis and retinal haemorrhages.

The remaining child (R. M.) was similar to the three cases described above except that she had gross haematuria for four weeks before admission. This child had severe anaemia on admission (see table 6) and died eight days later. She had a reticulocytosis of 5 per cent., the non-protein nitrogen was 142·8 mgm. per cent. and the serum protein 7·23 gm. per cent., the red cell volume was 24·3 per cent. and the indirect van den Bergh reaction amounted to only 1 unit. The blood pressure was 190/130 mm. Hg. The child's urine was bright red with fresh blood. The post-mortem examination on this girl disclosed a long standing chronic nephritis with a small atrophic right kidney and a large left kidney. There were developmental abnormalities in the vascular system of the right kidney with stenosis of the right renal artery.

Reference to table 6 shows that in this series of patients with nephrosclerosis no conspicuous anaemia has been found in the absence of haemorrhage and accordingly we cannot agree with the suggestion of Parsons and Ekola-Strolberg (1933) that anaemia and azotaemia are closely related. That there is no interference with haemopoiesis in this type of nephritis is well shown by two of these patients, E. D. and R. M. In the first the red cell count was over five millions per c.mm. in October (table 7). About three weeks later several carious teeth were extracted and during that night she had a severe haemorrhage from the tooth sockets, and in the course of the next few days her red cell count fell below 3 millions per c.mm. She developed an immediate reticulocyte

TABLE 7

THE BLOOD FOLLOWING HAEMORRHAGE IN CHRONIC INTERSTITIAL NEPHRITIS

NAME	DATE	RED CELLS PER C.MM.	Hb. PER CENT. (HALDANE)	R.B.C. VOL. PER CENT.	WHITE CELLS PER C.MM.	RETICULOCYTES PER CENT. OF R.B.C.
E. D.	16.10.37	5,330,000	99	41	—	—
	11.11.37	2,970,000	58	24	11,800	4·6
	25.11.37	4,025,000	80	33	10,800	3·2
R. M... ..	24.2.38	2,460,000	50	24·3	11,200	5·0

response of 4 to 5 per cent. and within two weeks her count had risen from below 3 millions to over 4 millions per c.mm. and her haemoglobin from 58 to 80 per cent. She then left hospital and further examination was impossible.

In the second (R. M.), who had gross haemorrhage from the renal pelvis producing a severe anaemia, the blood contained 5 per cent. of reticulocytes when the patient was almost moribund, a finding which excludes the possibility of marrow aplasia (table 7).

Chronic haemorrhagic nephritis. (Tables 8 and 9). The five patients in this group were all suffering from a chronic form of nephritis. In four cases there was a clear account of an initial attack of acute nephritis with haematuria, oedema and constitutional upset. In the other case (P. C.) the illness dated from an attack of pneumonia eight months before admission. He was known to have albuminuria immediately after the pneumonia.

All of these children had albuminuria, haematuria, and numerous casts in their urine. The systolic blood pressure was not greatly increased, ranging from 120 to 130 mm. Hg, there was a moderate degree of azotaemia, and oedema that varied in amount from time to time.

The cases in this group are considered to constitute an entirely different disease from nephrosclerosis (van Slyke et al. 1930). They differ from it in that the disease began as an apparently simple acute nephritis which passed into a subacute and chronic stage with haematuria, oedema and only moderate hyperpiesia. In nephrosclerosis, on the other hand, the onset is insidious, there is never any haematuria and never oedema and there is, except in renal dwarfism, a very high blood pressure with associated retinal changes. Brief notes on the five cases indicate the main clinical findings and the chronic nature of the disease.

M. R. Female, aged 5 years. Admitted 8.9.38, discharged 3.4.39. Recurrent tonsillitis during the past year; frequency of micturition and enuresis for past month. Two weeks before admission tonsillitis and swelling of face with haematuria during past four days and vomiting for one day.

On admission. The child had puffy eyes and oedema of the shins. The urine was loaded with albumin and moderate haematuria was found. Three weeks later she suffered from catarrhal jaundice which lasted for ten days. Thereafter there was no oedema, but haematuria continued as before. Some haemorrhage from tooth sockets occurred during the first week in October. Special investigations began on 18.10.38 when the following data were recorded:

Red blood cells	2,190,000 per c.mm.
White blood cells	11,100 per c.mm.
Haemoglobin	42 per cent.
Colour index	1·0.
Red blood cell volume	25·0 per cent.
Non-protein nitrogen	49·5 mgm. per cent.
Serum protein	6·72 gm. per cent.
Blood pressure	112/84 mm. Hg.
Reticulocytes	14·0 per cent.
Van den Bergh	0·5 units.

URINE—ALBUMIN	1·0 parts.
BLOOD	942 cells per c.mm.
VOLUME	440 c.c.

Thereafter her general health remained unchanged with albuminuria and haematuria persisting until she was discharged on 3.4.39. Haematinic treatment was rather ineffectual as may be seen from the findings on discharge:

RED BLOOD CELLS	3,425,000 per c.mm.
WHITE BLOOD CELLS	11,800 per c.mm.
HAEMOGLOBIN	62 per cent.
COLOUR INDEX	0·9.
RED BLOOD CELL VOLUME	35·8 per cent.
NON-PROTEIN NITROGEN	48·1 mgm. per cent.
SERUM PROTEIN	8·13 gm. per cent.
BLOOD PRESSURE	120/70 mm. Hg.
RETICULOCYTES	2·6 per cent.
URINE—ALBUMIN	Trace.
BLOOD	339 cells per c.mm.
VOLUME	770 c.c.

P. C. Male, aged 7 years. Admitted 7.11.38, discharged 5.4.39.

HISTORY. Whooping cough at 2½ years. Scarlet fever at 3 years. Chicken pox at 3½ years. Measles at 4 years. Diphtheria at 4½ years. In March, 1938, he had pneumonia and was in hospital for two months, and since then had albuminuria, face puffy in mornings and occasional swelling of feet.

ON ADMISSION. Slight oedema was found. His tonsils were moderately enlarged and unhealthy. These were removed in January, 1939. The blood and urine findings were as follows:

RED BLOOD CELLS	4,035,000 per c.mm.
WHITE BLOOD CELLS	11,400 per c.mm.
HAEMOGLOBIN	70 per cent.
COLOUR INDEX	0·9.
RED BLOOD CELL VOLUME	36·4 per cent.
RETICULOCYTES	2·9 per cent.
NON-PROTEIN NITROGEN	41·0 mgm. per cent.
SERUM PROTEIN	5·49 gm. per cent.
BLOOD PRESSURE	134/80 mm. Hg.
URINE—ALBUMIN	4·0 parts.
BLOOD	12 cells per c.mm.
VOLUME	1240 c.c.

Oedema gradually disappeared, but otherwise his condition remained more or less unchanged. The reticulocyte count varied between 0·6 per cent. and 3·1 per cent., but in spite of treatment with iron, liver and ascorbic acid anaemia persisted. On 4.4.39 the following blood and urine findings were recorded:

RED BLOOD CELLS	4,050,000 per c.mm.
WHITE BLOOD CELLS	11,000 per c.mm.
HAEMOGLOBIN	76 per cent.
COLOUR INDEX	0·9.
RED BLOOD CELL VOLUME	38·8 per cent.
RETICULOCYTES	0·8 per cent.
NON-PROTEIN NITROGEN	58·8 mgm. per cent.
SERUM PROTEIN	5·90 gm. per cent.
BLOOD PRESSURE	124/68 mm. Hg.

Urine contained albumin and blood as before; its volume was approximately 1020 c.c.

J. C. Male, aged 5 years. Admitted 29.4.38, discharged 29.9.38.

HISTORY. Swelling of abdomen for two years. Frequent attacks of tonsillitis. On 15.4.38 the urine was noted to be dark red and two days before admission the child became ill and out of sorts.

ON ADMISSION. Slight oedema was found which gradually improved; there was moderate ascites. When first investigated on 19.7.38 the blood and urine examination gave the following results :

RED BLOOD CELLS	2,440,000 per c.mm.
WHITE BLOOD CELLS	6400 per c.mm.
HAEMOGLOBIN	44 per cent.
COLOUR INDEX	0·9.
RED BLOOD CELL VOLUME	25·4 per cent.
RETICULOCYTES	0·6 per cent.
NON-PROTEIN NITROGEN	57·5 mgm. per cent.
SERUM PROTEIN	5·09 gm. per cent.
BLOOD PRESSURE	100/70 mm. Hg.
URINE—ALBUMIN	4·5 parts.
BLOOD	400 per c.mm.
VOLUME	770 c.c.

Oedema disappeared, but ascites and haematuria persisted and his general condition had not improved on transfer to another hospital on September 29, 1938. On 30.8.38 the blood and urine examination gave the following results:

RED BLOOD CELLS	2,990,000 c.mm.
WHITE BLOOD CELLS	12,200 per c.mm.
HAEMOGLOBIN	52 per cent.
COLOUR INDEX	0·9.
RED BLOOD CELL VOLUME	29·8 per cent.
RETICULOCYTES	0·5 per cent.
NON-PROTEIN NITROGEN	45·4 mgm. per cent.
SERUM PROTEIN	7·11 gm. per cent.
BLOOD PRESSURE	108/70 mm. Hg.
URINE—ALBUMIN	1·75 parts.
BLOOD	2448 cells per c.mm.
VOLUME	450 c.c.

A. A. Female, aged 8 years. Admitted 22.10.37, discharged 30.6.38.

Scarlet fever and ill for six months at age of seven years. In April, 1937, her face became puffy and later legs and arms. Five weeks before admission she had a febrile illness and swelling became more marked.

ON ADMISSION. Well-marked oedema and moderate haematuria were present. The state of the blood and urine was as follows:

RED BLOOD CELLS	3,625,000 per c.mm.
WHITE BLOOD CELLS	13,600 per c.mm
HAEMOGLOBIN	68 per cent.
COLOUR INDEX	0·9
RED BLOOD CELL VOLUME	29·0 per cent.
RETICULOCYTES	1·1 per cent.
NON-PROTEIN NITROGEN	28·7 mgm. per cent.
SERUM PROTEIN	5·25 gm. per cent.
BLOOD PRESSURE	124/78 mm. Hg.

URINE—ALBUMIN	2·0 parts.
BLOOD	691 cells per c.mm.
VOLUME	520 c.c.

Oedema slowly disappeared only to come and go later and the general condition remained more or less stationary. In spite of haematinic therapy the following figures show that on 16.6.38 the condition of the blood had deteriorated.

RED BLOOD CELLS	2,970,000 per c.mm.
WHITE BLOOD CELLS	7800 per c.mm.
HAEMOGLOBIN	58 per cent.
COLOUR INDEX	1·0.
RED BLOOD CELL VOLUME	31·4 per cent.
RETICULOCYTES	1·7 per cent.
NON-PROTEIN NITROGEN	23·9 mgm. per cent.
SERUM PROTEIN	4·62 gm. per cent.
BLOOD PRESSURE	118/78 mm. Hg.

URINE—ALBUMIN	2·0 parts.
BLOOD	126 cells per c.mm.
VOLUME	900 c.c.

J. S. Male, aged 9 years. Admitted 28.7.37, discharged 17.1.38.

Two weeks before admission his face became puffy and he complained of anorexia and listlessness. One week before admission oedema became widespread and severe.

ON ADMISSION. There was general anasarca and ascites, and much blood and albumin in urine. His blood pressure was not raised. Non-protein nitrogen was 39 mgm. per cent. Serum protein was 5·45 gm. per cent. In August an effusion developed in both pleura. During September and October the oedema and ascites increased greatly, but at the end of October gradually began to subside. Special examination of the blood began on October 18, when the following findings were recorded:

RED BLOOD CELLS	3,380,000 per c.mm.
WHITE BLOOD CELLS	9200 per c.mm.
HAEMOGLOBIN	67 per cent.
COLOUR INDEX	1·0.
RED BLOOD CELL VOLUME	31·0 per cent.
SERUM PROTEIN	5·51 gm. per cent.

URINE—ALBUMIN	—
BLOOD	—
VOLUME	340 c.c.

By December the oedema and ascites had disappeared and the urine had become free from blood. Examination of the blood and urine on 9.12.37 gave the following results:

RED BLOOD CELLS	3,735,000 per c.mm.
WHITE BLOOD CELLS	14,200 per c.mm.
HAEMOGLOBIN	68 per cent.
COLOUR INDEX	0·9.
RED BLOOD CELL VOLUME	35·0 per cent.
NON-PROTEIN NITROGEN	72·5 mgm. per cent.
SERUM PROTEIN	5·96 gm. per cent.
BLOOD PRESSURE	110/68 mm. Hg.

URINE—ALBUMIN	4 parts.
BLOOD	Nil.
VOLUME	1200 c.c.

It is in this group, and in this group only, that the characteristic anaemia of nephritis has been found to occur. The difference between the blood findings in this group shown in table 8 and those in the other groups (tables 2, 4 and 6) is striking. In this type of the disease there is a considerable anaemia with a slightly greater reduction in the haemoglobin percentage than in the number of red cells giving a colour index of 0·9. The mean corpuscular volume is 95 cubic microns indicating that the cells are of normal size or slightly larger than normal, a finding in agreement with that of Townsend, Massie and Lyons (1937). Observations made two to three months later (table 8) show practically no change in the state of the blood in spite of active treatment both with iron and liver. Thus in this group there is a moderately severe normocytic or megalocytic anaemia which may be described as orthochromic and which is not materially influenced by treatment.

TABLE 8

THE BLOOD IN CHRONIC HAEMORRHAGIC NEPHRITIS

SOON AFTER ADMISSION TO HOSPITAL					2 TO 3 MONTHS AFTER ADMISSION TO HOSPITAL				
NAME	RED CELLS PER C.MM.	Hb. PER CENT. (HALDANE)	WHITE CELLS PER C.MM.	R.B.C. VOL. PER CENT.	NAME	RED CELLS PER C.MM.	Hb. PER CENT. (HALDANE)	WHITE CELLS PER C.MM.	R.B.C. VOL. PER CENT.
P. C. ..	4,035,000	70	11,400	36·4	P. C. ..	3,985,000	76	12,400	38·2
M. R...	2,190,000	42	11,100	25·0	M. R. ..	2,540,000	50	11,700	28·6
J. C. ..	2,440,000	44	6,400	25·4	J. C. ..	2,990,000	52	12,200	29·8
A. A. ..	3,625,000	68	13,600	29·0	A. A. ..	3,000,000	60	8,300	30·0
J. S. ..	3,735,000	68	14,200	35·0	J. S. ..	Dismissed	from	hospital	
Average	3,205,000	58	11,320	30·2	Average	3,129,000	59	11,500	31·6
Average colour index, 0·90. Average mean corpuscular volume, 94 c. microns.					Average colour index, 0·94. Average mean corpuscular volume, 101 c. microns.				

From table 8 it will be seen that there was a moderate leucocytosis. Films showed the red cells to be well coloured and fairly uniform in size. The differential counts on four of these children are recorded in table 9. No abnormal red or white cells were seen. All the children showed some degree of lymphocytosis and one of them had an eosinophilia of 3·5 per cent. The number of reticulocytes was variable, but never amounted to less than 0·5 per cent. of the red cells. It is interesting to note that these children had a moderate leucocytosis and a normal or increased reticulocyte count, whereas idiopathic aplastic anaemia, with which this disease is so often compared, is associated with leucopenia and the absence of reticulocytes.

TABLE 9

DIFFERENTIAL COUNTS OF NUCLEATED CELLS IN A GROUP OF CHILDREN WITH CHRONIC HAEMORRHAGIC NEPHRITIS

NAME	NEUTROPHIL POLYMORPHS	BASOPHIL POLYMORPHS	EOSINOPHIL POLYMORPHS	METAMYELOCYTES	LYMPHOCYTES	NORMOBLASTS	MYELOCYTES	RETICULOCYTES	
								HIGHEST	LOWEST
P. C. ..	47	0	1·0	9	43	0	0	3·1	0·8
M. R. ..	46	0·5	0·5	3	50	0	0	14·0	0·5
J. C. ..	60	0	0	2	38	0	0	0·6	0·5
A. A. ..	46	0·5	3·5	5	45	0	0	2·6	0·6

Figures are per cent. of all white cells except reticulocytes which are per cent. red cells.

Discussion

The results appear to show that both in the nephrotic syndrome and in acute haemorrhagic nephritis there are definite changes in the concentration of certain constituents of the blood, but that there is no evidence that either disease produces any absolute diminution in the number of red cells or in the haemoglobin content. In nephrosis the concentration reaches its height during the period of oliguria and when oedema is pronounced, whereas in acute haemorrhagic nephritis it reaches its maximum during active diuresis and when oedema is subsiding. As a possible explanation of these paradoxical reactions it may be suggested that in nephrosis the secretory power of the kidney is not impaired but that blood concentration is brought about by leak of fluid from the vascular system into the tissues producing oedema. Whether this is due to increased permeability of endothelial tissue or solely to alterations in osmotic pressure it is impossible to say. In acute nephritis, on the other hand, the excretory power of the kidney is impaired, but blood dilution is prevented by passage of excess fluid into the tissues. When diuresis begins in this type of the disease haemoconcentration occurs because fluid is withdrawn from the vascular system by the kidneys more quickly than it can be replenished from the oedematous tissues.

It is important to bear in mind these fluctuations in the red cell counts and haemoglobin percentage before deciding on the presence or absence of anaemia and the efficacy of the treatment of the anaemia. In the nephrotic syndrome any anaemia that may be present will be masked during increasing oedema by haemocc ncentration, and the true state of the blood will only become manifest during a non-oedematous phase. On the other hand, in acute nephritis serial counts done when the patient is recovering and when the first flood of diuresis has ceased will reveal what appears to be an increasing anaemia, but is in reality only a diminishing hemoconcentration. Not until four or five weeks after oedema has disappeared does the red cell count reflect the true state of the blood. Any further reduction after this would indicate a true progressive anaemia.

Contrary to the findings of other workers this investigation has failed to demonstrate anaemia in nephrosclerosis in the absence of such complicating factors as haemorrhage.

It seems that only in chronic haemorrhagic nephritis is there true anaemia. It is orthochromic and normocytic. Its cause is difficult to explain. It might be suggested that the anaemia in this type of nephritis is due to loss of blood through the kidney, but this is improbable as the amount of blood lost is extremely small and chronic haemorrhage should lead to anaemia of the hypochromic type. The fact that treatment with iron is of no avail provides additional evidence that it is not due to blood loss. Furthermore, it does not appear to be due to marrow aplasia for there is no diminution in the number of white cells and reticulocyte counts are within normal limits.

Conclusions

(1) Previous work on anaemia in nephritis is discussed.

(2) In oedematous patients blood obtained by puncture of the lobe of the ear is slightly diluted, but the errors arising in doing counts from blood obtained by vene-puncture are greater than those arising from skin puncture, and the latter method is therefore preferable.

(3) During the stage of increasing oedema and oliguria in nephrosis and during the stage of diminishing oedema and active diuresis in acute nephritis there is blood concentration. In neither of these types of nephritis is there more than slight anaemia.

(4) When certain acute infections occur in the course of nephrosis rapid and severe anaemia results and after effective treatment of the infection the blood quickly returns to normal.

(5) Anaemia is not characteristic of nephrosclerosis in the absence of haemorrhage, and when this occurs there is evidence of active haemopoiesis.

(6) In chronic haemorrhagic nephritis there is often severe orthochromic normocytic anaemia with a normal or slightly increased number of reticulocytes and mild leucocytosis. The blood picture is not that of aplastic anaemia. No treatment that will influence the condition is known. It is only in this type of nephritis that true anaemia has been found.

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A FURTHER INVESTIGATION OF BREAST-FEEDING

A STUDY OF ONE THOUSAND MOTHERS

BY

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The following investigations were undertaken in order to find the cause of the variation in the breast-feeding rate which, in a previous paper (Robinson, 1939), was shown to occur from year to year.

TABLE I

PERCENTAGE OF INFANTS BREAST-FED FOR ONE, THREE, SIX AND NINE MONTHS, SHOWN IN RELATION TO MONTH IN WHICH BORN

DURATION OF BREAST-FEEDING IN MONTHS	JAN.	FEB.	MAR.	APR.	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
One	43	32	39	49	40	37	49	41	44	39	45	41
Three	24	24	18	25	19	19	17	22	29	19	25	31
Six	3	0	14	6	12	14	8	21	6	6	5	11
Nine	30	44	29	20	29	30	26	16	21	36	25	17
Numbers used ..	46	41	62	55	58	57	47	56	48	31	40	46

The breast-feeding rate for 1937 was re-assessed monthly according to the date on which the babies were born. Table 1 shows that the swing is still present and has no relation to the seasons of the year. The percentage of babies still on the breast at the ninth month is highest (44 per cent.) for those born in February, and lowest (16 per cent.) for those born in August. April and July give the highest (49 per cent.) and February the lowest (32 per cent.) percentage weaned during the first month. The duration of breast-feeding was calculated for 3,515 babies in accordance with the position of the child in the family, judged by the parity of the mother and not by the number of living children in the family at the time when the child was first seen. Table 2 shows the month of weaning of 3,515 babies classified according to their position in the family judged by the parity of the mother, and shows percentages weaned by the end of the first, third and seventh months and those still left on the breast during the eighth month. Families of nine or more children were too few to analyse. It appears from table 2 that the position of the child in

TABLE 2

BABY	PERCENTAGE DEAD	PERCENTAGE WEANED				TOTAL	DISCARDED	USED
		1 MONTH	2–3 MONTHS	4–7 MONTHS	8 MONTHS			
1st	7	20	15	8	57	1,050	91	959
2nd	11	19	10	8	63	827	87	740
3rd	11	19	12	7	63	640	71	569
4th	12	20	10	6	64	482	59	423
5th	13	23	12	6	59	369	48	321
6th	16	20	13	3	64	265	42	223
7th	17	20	14	5	61	200	34	166
8th	20	19	9	6	57	130	26	114

the family has no effect on the duration of breast-feeding. Those discarded include still-births, defaulters, and those who died before the end of lactation. The second column gives the percentage of still-births plus babies dying while still on the breast. The death-rate increases with the parity of the mother. Yerushalmy (1940) noticed that still-births increased as the number of pregnancies increased. On further investigation, I found that thirty-one deaths occurred over the age of three months, but they did not seem to increase with the parity of the mother, whereas the 171 deaths which occurred between birth and three months increased with the parity of the mother, so that the death-rate against the eighth born is twice that of the first born. It would, therefore, appear that whatever governs still-births and miscarriages also affects the viability of babies under three months of age even though they are breast-fed. Seibert (1940) suggests the cause of neonatal deaths to be the biological factor of constitution.

TABLE 3

MONTH OF WEANING OF THE ONLY CHILDREN OF 300 MOTHERS, ASSESSED ACCORDING TO THE AGE OF THE MOTHER. (PERCENTAGES WEANED BY THE END OF THE FIRST, THIRD, SIXTH AND NINTH MONTHS)

AGE OF MOTHER	PERCENTAGE OF INFANTS WEANED				TOTAL
	1 MONTH	3 MONTHS	6 MONTHS	9 MONTHS	
Under 20 years	28	13	10	49	39
20–25 years ..	28	20	6	46	149
25–30 ,, ..	21	18	11	50	89
30–35 ,, ..	42	5	11	42	19
35–40 ,, ..	0	0	25	75	4

The breast-feeding of 300 babies of mothers attending the antenatal clinic for their second pregnancy was examined in order to see if the age of the mother affected the feeding of her first child. Table 3 shows a negative result. Almost the same percentage of mothers of between thirty and thirty-five years of age

feed their babies for nine months as do the younger mothers, although they are inclined to wean oftener in the first month. The thirty-five to forty year old group is small, but suggests that age has no adverse effect on lactation.

The histories of all the lactations of 1,369 cases were collected (table 4). 369 were discarded because they had only one child. The remaining 1,000 were divided into four types as follows:

Type I in which all the children were fully breast-fed.

Type II in which all the children were weaned early.

Type III in which the older children were weaned early and many of the younger ones were fully breast-fed.

Type IV in which the older children were fully breast-fed and many of the younger ones were weaned early.

TABLE 4

THE FIGURES IN BRACKETS INDICATE THE PERCENTAGE TYPE ACCORDING TO SIZE OF FAMILY

TYPE OF MOTHER	SIZE OF FAMILY IN EACH TYPE														PERCENTAGE IN EACH TYPE	TOTAL
	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
I	113 (43)	82 (40)	56 (41)	55 (40)	39 (43)	25 (38)	23 (45)	15 (50)	2 (18)	0	3 (60)	—	—	—	41·3	413
II	87 (33)	56 (28)	31 (22)	24 (18)	15 (16)	6 (9)	9 (18)	4 (13)	3 (27)	0	2 (40)	0	1 (100)	—	23·8	238
III	33 (13)	26 (13)	25 (18)	14 (10)	9 (10)	9 (14)	9 (18)	2 (7)	1 (9)	—	—	—	—	—	12·8	128
IV	30 (11)	38 (19)	26 (19)	44 (32)	28 (31)	26 (39)	10 (19)	9 (30)	5 (46)	2 (100)	0	2 (100)	—	1 (100)	22·1	221
Total Families	263	202	138	137	91	66	51	30	11	2	5	2	1	1	—	1,000

Table 4 shows the number of families, their size and the type to which they belong. Forty-one per cent. of mothers feed all their babies to nine months or over; about 24 per cent. wean all their babies during the first few months, about 13 per cent. wean their elder children during the first few months, but usually succeed in feeding most of the younger ones to nine months; and 22 per cent. feed their elder children to nine months, but usually wean the younger ones during the first few months. Type I mother is found in 43 per cent. of families of two children and this percentage only varies between 43 per cent. and 38 per cent. up to families of seven children. Type II mother is found in 33 per cent. of families of two children and this percentage gradually declines to 9 per cent. in families of seven children, i.e. as the family grows larger the type II mother changes to type III. Type III mother is found in 13 per cent. of families of two children and as the size of the family increases the percentage varies between 10 per cent. and 18 per cent. Type IV mothers

are found in 11 per cent. of families of two children and this percentage increases to 39 per cent. in families of seven children. This may have given rise to the belief that older women do not feed so long as the younger ones. I have shown above that this is not the case. The total number of families of eight children and over are so small that the percentages may not be accurate. In each of the types II, III and IV 52 per cent. of the weaning occurred before the end of the first month, and 80 per cent. before the end of the third month.

TABLE 5

THE PERCENTAGE OF THE FOUR TYPES OF MOTHER OCCURRING IN THE YEARS 1936, 1937 AND 1938, TOGETHER WITH THE WEANING-RATE OF EACH YEAR GIVEN IN PERCENTAGES OF THOSE WEANED AT THE END OF THE FIRST, THIRD, SIXTH AND NINTH MONTHS

YEAR	TYPE OF MOTHER (PER CENT.)				TOTAL	PERCENTAGE OF INFANTS WEANED			
	I	II	III	IV		1 MONTH	3 MONTHS	6 MONTHS	9 MONTHS
1936	42	21	12	25	157	25	14	7	54
1937	46	16	12	26	160	22	15	6	57
1938	41	16	10	33	103	18	23	6	53

Table 5 shows that the swing in the breast-feeding rate during 1936, 1937 and 1938 is caused by the variation in percentages of pregnancies occurring in the four types of mother in each year, e.g. 1937 contained the highest number of type I mothers and also the highest number of babies on the breast at nine months, whereas 1938 contained the lowest number of type I mothers and the lowest number on the breast at nine months. To prove that breast-feeding is really declining, it would be necessary to show that, over a number of years, a steady decrease had occurred in the percentage of type I mother together with an increase in that of the other three types. Table 5 had to be compiled from the antenatal cards on which I had written the breast-feeding histories. The result as a whole is higher than that obtained in my first paper (Robinson, 1939) which may be accounted for by the fact that mothers usually give the time when breast-feeding ceases altogether and not, as I did, the time when the first bottle was given. This factor may also give the actual observer of breast-feeding the idea that the last generation of mothers (from whom histories only are available) were better feeders than those of this generation.

Table 6 deals with the physique of the mother. It shows that lactation is affected, not by the gross size of the breasts, but by the size and character of the nipple. The actual breast tissue is impossible to assess as it is surrounded by so much fat. In the flat-chested mothers one can feel a firm, circular, movable plaque attached to the nipple, which increases during the first twenty weeks of pregnancy. The presence of secretion (either watery or like thick cream) was demonstrated in both type I and type II mothers as early as the twenty-sixth week of pregnancy. It occurred antenatally in 36 per cent. of type I mothers, and in 27 per cent. of type II mothers. Its presence, therefore, is no

criterion that the subsequent baby will be fully breast-fed. Lactorrhoea also occurs in both type I and type II mothers. Mastitis tends to increase in type II and type IV mothers. It is difficult to say whether this is due to advice to refrain from feeding or due to the inability to feed. Breast abscesses cause an increase in type II and type IV mothers as well as a considerable reduction in type I mothers.

TABLE 6

THE PERCENTAGE OF MOTHERS IN EACH OF THE FOUR TYPES GROUPED ACCORDING TO THEIR PHYSICAL CHARACTERISTICS, COMPARED WITH THE PERCENTAGES OF THESE GROUPS NOTED IN TABLE 4

TYPE &	TABLE 4	NIPPLES							BREASTS						GENERAL CONDITION			
		FLAT	SMALL	AVERAGE	LARGE	LOOSE	TIED	CRACKED	FLAT	SMALL	AVERAGE	LARGE	ABSCESS	MASTITIS	ENLARGED THYROID	RHEUMATIC HEART	MASCULINITY *	OBESITY
I	41	18	28	48	46	45	16	28	43	41	48	41	16	28	30	39	31	56
II	24	64	56	30	20	28	56	43	21	27	23	23	40	36	30	32	47	24
III	13	0	7	10	10	11	12	14	11	14	12	14	9	0	10	10	14	0
IV	22	18	9	12	24	16	16	15	25	18	17	22	35	36	30	19	8	20
Total	1,000	17	113	535	105	133	32	58	103	305	267	148	43	14	10	31	51	25

* The term masculinity is applied to those women who had varying degrees of the male distribution of hair.

Mothers with flat or small nipples are not as good feeders as those with average or large nipples. A baby can be successfully fed with a flat nipple provided it is ' loose ' and not ' tied,' i.e. when the baby chews with its gums on the outer edge of the areola the nipple is not retracted. If the first finger and thumb are used in place of the baby's upper and lower jaws, a thick cord is felt pulling on a ' tied ' nipple; the nipple is pulled in and a bead of milk appears. Whereas with the ' loose ' nipple the finger and thumb come easily together and a squirt of milk comes out, just as if the bulb of an enema syringe had been squeezed. The size and the distance covered by the jet depends on the force and rapidity used in this pincer movement, as well as the fact that it is used on the outer margin of the areola. Babies with powerful masseter muscles are called strong suckers by their mothers. There is a high incidence of ' tied ' nipples among mothers suffering from cracked nipples and breast abscesses. It can be seen in table 6 that ' tied ' nipples reduce the percentage of type I mothers, and increase that of type II mothers to almost as great an extent as do flat nipples. Cracked nipples also reduce the length of lactation, but not to quite the same degree.

Among the ten cases of enlarged thyroid glands, two were cases of exophthalmic goitre, and they belonged to type IV. Possibly their older

children were born before their thyroid gland was affected. One mother had had partial removal of her thyroid gland at puberty, and fed both her babies. The others were just simple enlargements. Mothers with rheumatic endocarditis are usually good feeders if not forbidden to feed by their medical attendant. The masculine woman belongs mostly to type II, whereas the very obese woman (12–14 stone) is found mostly in type I.

TABLE 7

THE PERCENTAGE OF MOTHERS IN EACH OF THE FOUR TYPES GROUPED ACCORDING TO THEIR ANTENATAL HISTORY

TYPE OF MOTHER	TABLE 4	MORNING SICKNESS				HEART-BURN		VARICOSE VEINS		PRE-ECLAMPSIA	PYELITIS	APPARENT CALCIUM DEFICIENCY †
		AMESIS	SLIGHT *	AVERAGE	HYPEREMESIS	MILD	SEVERE	SLIGHT	SEVERE			
I	41	57	60	40	13	45	39	49	38	47	32	46
II	24	29	28	34	71	29	44	29	38	30	38	32
III	13	5	7	11	3	11	6	5	11	4	9	8
IV	22	9	5	15	13	15	11	17	13	19	21	14
Total	1,000	242	72	484	63	342	18	111	129	70	68	305

* This includes nausea without vomiting.
† This includes antenatal symptoms such as cramps and generalized pruritus, which are relieved by calcium.

Table 7 deals with the antenatal histories of the four types of mother. Morning sickness and pyelitis seem to be the only pre-natal complaints which have an adverse effect on breast-feeding. The greater the severity of the morning sickness, the shorter the lactation and vice versa. Masculinity is associated with morning sickness, since only 4 per cent. had amesis and 28 per cent. of 861 mothers had hyperemesis. This may be the reason why so many masculine women belong to type II. The numbers of cases of excessive heartburn are too small to be considered. In the pre-eclamptic group six mothers developed eclampsia; three belonged to type I and three to type II. Severe varicose veins increase slightly the percentage of type II mothers at the expense of type I.

An enquiry into the time when the mothers' periods recommenced after labour showed that 24 per cent. of mothers of both type I and type II had their first period when their babies were six weeks old; also that 59 per cent. of type I mothers and 68 per cent. of type II mothers did not have any periods until after weaning had taken place. It seems, therefore, that the return of menstruation has no effect on lactation, and can occur regularly during the nine months of breast-feeding.

Summary

An investigation was carried out in order to find the cause of the swing in the breast-feeding rate. Mothers were classified into four types. The parity, age, physical characteristics and antenatal history of the mothers were examined in relation to breast-feeding.

Conclusions

(1) Four types of mother are described.

(2) The swing in the breast-feeding rate depends on the variations in the percentage of these types.

(3) Breast-feeding is not affected by the following: the seasons of the year, the parity of the mother, the age of the mother, the size of the breasts, the antenatal presence of secretion in the breasts, the return of menstruation, rheumatic endocarditis, simple enlargement of the thyroid gland, pre-eclampsia, and antenatal symptoms relieved by calcium.

(4) Breast-feeding is affected by the following: the size and character of the nipple, masculinity, obesity, morning sickness, pyelitis, severe varicose veins, breast abscesses and cracked nipples.

(5) Fifty-two per cent. of early weaning occurs in all types before the end of the first month.

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INFANTILE MUSCULAR ATROPHY OF SPINAL ORIGIN

A REPORT OF TWO CASES

BY

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Two cases of infantile muscular atrophy of spinal origin were admitted in the summer of 1940 to the wards to which we were attached in the Royal Hospital for Sick Children, Edinburgh. They are considered of sufficient interest to be published in detail.

Review and discussion of literature

In 1891 Werdnig described cases of muscular atrophy in infants characterized by wasting and paralysis of the muscles of the trunk, neck and proximal limb segments, beginning about the tenth month of life. Tendon reflexes were lost. Bulbar symptoms, fibrillary twitchings and secondary contractures were present in some cases. There was no impairment of sensation or of mental development. Other children of the same family were affected. The disease ran a rapidly fatal course, and at autopsy the anterior horn cells were found to be atrophied, and secondary simple atrophy of the paralysed muscles was present. In 1893 Hoffmann confirmed Werdnig's description, and since then cases of this type have been known as examples of Werdnig-Hoffmann's disease. In 1900 Oppenheim described a syndrome characterized by a loss of power in all the muscles of the body. The muscles were small, hypotonia was marked, and contortionist attitudes possible. There were no localized atrophic areas as in the Werdnig-Hoffmann disease. Oppenheim's cases were further distinguished by being present from birth, by the absence of any familial involvement, and by a tendency to improve. Cases of this type are called Oppenheim's disease, amyotonia congenita, or myatonia congenita. Numerous other cases have since been described and much discussion has arisen about the features differentiating the two diseases. It has been found extremely difficult to determine constant distinguishing features.

Many different authorities, including Huenekens and Bell (1920), Greenfield and Stern (1927), Paterson (1928), and Tuthill and Levy (1931) have come to the conclusion that Werdnig-Hoffmann's and Oppenheim's diseases have an identical pathological basis, and that no sharp line of differentiation is possible clinically. The two probably represent extreme types of a disease in which many variations are possible.

It would appear undesirable therefore to continue to attempt to divide cases of muscular atrophy in infancy into cases of Werdnig-Hoffmann's disease

and Oppenheim's disease. Garrod, Batten, Thursfield and Paterson (1934) use the term infantile muscular atrophy of spinal origin to cover all types of case of this kind.

From a consideration of the findings in many cases described under the headings Werdnig-Hoffmann's disease and Oppenheim's disease, the following broad outline of the outstanding features of infantile muscular atrophy of spinal origin may be given:

(a) The disease is present at birth or develops gradually during the early months of life.
(b) A familial incidence is common.
(c) The sexes are equally affected.
(d) Muscle wasting may be generalized or may be more prominent in certain areas, particularly in the trunk, neck and proximal limb segments. It is often obscured by a thick layer of subcutaneous fat.
(e) The muscles are hypotonic, markedly so in some cases, and the tendon reflexes are lost.
(f) Paralysis of the intercostal muscles is common. Secondary results are a prominent abdomen, a weak cry, laboured coughing, and difficulty in sucking.
(g) Rarely cranial nerve palsies occur.
(h) Some cases develop contractures.
(i) Sensation and mentality are unimpaired in all cases.
(j) The prognosis is poor. The majority die in a few months from pneumonia. A small number, especially the congenital type with a good family history, and no local wasting, tend to improve.
(k) At autopsy the findings are atrophy of anterior horn cells, and secondary atrophy of muscle.

That the position may not be as simple as is indicated above is suggested by the cases presented by Turner (1940), which showed a gradual transition from a state of amyotonia with marked flaccidity and absence of local muscular atrophy to a state of myopathy with local muscular atrophy and absence of flaccidity. As a number of cases of Oppenheim's disease have been reported (Lereboullet and Baudouin, 1909; Councilman and Dunn, 1911; Haushalter, 1920; Silverberg, 1923; and Menges, 1931) in which no evidence of any spinal cord lesion was discovered in spite of careful search, Turner concludes that ' as was indicated by Spiller (1914), amyotonia congenita is a symptom rather than a disease, and it may be caused either by a congenital myopathy as in the family reported here, or by a spinal affection of unknown etiology which bears a close relation to Werdnig-Hoffmann's disease.'

If this conclusion is correct it is possible that the relatively few recorded cases which have improved considerably were myopathies rather than muscular atrophies. This is the type of case in which pathological confirmation will be difficult to obtain.

The etiology of muscular atrophy and of the myopathies is unknown.

Bicknell (1940) has reviewed recent work with vitamin E, which suggests that this factor may be important etiologically and therapeutically both in the

muscular atrophies and in the myopathies. Ringsted (1935) and Einarson and Ringsted (1938) feeding adult rats on a diet free from vitamin E found that there developed, after a period of fifteen weeks, ataxia of the hind legs which later became extreme. This was followed by flaccid paralysis and gross wasting. The condition of the rats was otherwise good. The pathological picture resembled a combination of tabes and progressive muscular atrophy, there being degeneration of the posterior roots, posterior columns and later of the anterior horn cells. Muscle degeneration was also present. Later work by Morgulis and Spencer (1936), Morgulis, Wilder and Eppstein (1938), Olcott (1938), and Madsen (1936), in addition to earlier work by Evans (1928), showed that this muscle degeneration may be a primary procedure in young animals. Regeneration of the wasted muscles occurred on addition of vitamin E to the diet. Bicknell suggests that the myopathies and amyotrophic lateral sclerosis may be interpreted as the same deficiency disease, the former occurring in children and the latter in adults. The same author suggests that a dietetic insufficiency of vitamin E may readily occur, and he claims good results in eighteen cases of muscular dystrophy, in four cases of amyotrophic lateral sclerosis, and in one case of amyotonia congenita treated with fresh dried whole wheat germ $\frac{1}{2}$ oz. twice daily. Bicknell states that it is important to realize that the anti-sterility factor—i.e. alpha tocopherol—is probably not identical with the myotrophic and neurotrophic factors (Goettsch and Ritzmann, 1939), though they all occur together in wheat germ oil. Wechsler (1940) also claims good results in cases of amyotrophic lateral sclerosis treated with vitamin E together with the vitamin B complex.

These claims, however, have not been substantiated by other workers, notably Shelden et al. (1940), Denker and Scheinman (1941), and Ferrebee et al. (1941). The position is therefore still obscure, but at present it would appear that treatment of cases of infantile muscular atrophy of spinal origin with vitamin E is well worth a trial. Should some of these cases, as Turner suggests, prove to be myopathies the same treatment would apply. It has been pointed out (Lancet, 1940, 1941) that as 'the amount of creatinine in the urine (on a creatine-free diet) depends on the amount of improperly functioning muscle, its estimation provides a convenient biochemical method of assessing therapy.' It is obvious, also, that an insufficiency of vitamin E in the maternal diet both in the ante-natal and in the post-natal periods is possibly an important factor in the etiology of infantile muscular atrophy of spinal origin.

Case reports

Case 1. G. S. Admitted aged 8 weeks.

HISTORY. Since birth the child had been unable to move any limb, apart from slight jerkings of the forearms and of the legs below the knees. The limbs were limp and held persistently in the same position, the arms being flexed across the chest, and the lower extremities extended. The child appeared to breathe with the abdomen only. There were no other complaints. The appetite was good. There was no difficulty in sucking or swallowing and no vomiting. The bowels were regular. There was no cough.

The mother's pregnancy was uneventful. Labour lasted two hours after the onset of severe pains. No instruments or anaesthetic were required. The child was temporarily cyanosed at birth. Breast feeding was not attempted because of difficulty with other children due to painful nipples and the infant was reared on a patent milk food with regular four-hourly feeds. No cod-liver oil or orange juice was given.

FAMILY HISTORY. Father, aged thirty-four years. Mother, aged twenty-six years. Children: (1) M., aged seven years. (2) F., aged six years.

(3) M., aged five years. (4) M., aged eight weeks, the patient. Parents and children were all alive and well. There were no miscarriages and no family history of paralysis or tuberculosis.

Examination. A poorly nourished, quiet baby. Weight 8 lb. 14 oz. Circumference of skull 15 in. Anterior fontanelle of normal tension and size. Right side of forehead more prominent than left. No palpable abnormality of limb bones or spine. Chest poorly formed, lower ribs in-drawn. Abdomen prominent. Skin of good colour and fine texture; warm and dry; no cyanosis or jaundice. Temperature 98·4° F. Pulse 150 per minute. Respiration 40 to 50 per minute.

LOCOMOTOR AND CENTRAL NERVOUS SYSTEM. No evidence of mental deficiency. Upper arm adducted, forearm flexed and pronated, hand flexed, fingers extended. Lower limbs extended, feet plantar flexed. The range of voluntary movement did not exceed 15° at any joint, whereas a full range of passive movement was easily effected. Marked protrusion of abdomen on inspiration; screening showed normal diaphragmatic movements; costal movements not reported, but clinically respiration appeared to be entirely diaphragmatic. Muscles hypotonic; no obvious atrophy; no fibrillation seen. These last two features may have been obscured by the subcutaneous fat.

Tendon reflexes absent. No sensory impairment detected. Pupils dilated, equal, central, circular, reacting to light and accommodation. No ptosis, strabismus, or nystagmus. No facial weakness, and no difficulty in sucking or swallowing.

Cerebrospinal fluid: clear and not under pressure; nothing pathological in stained film; protein 20 mgm. per cent.; sugar 76 mgm. per cent.; chlorides 714 mgm. per cent.

Clinical examination of the other systems failed to reveal any abnormality. x-ray of chest on admission showed both lungs normally aerated. There was no abnormality of cardio-vascular system.

PROGRESS. One week after admission the respiration rate increased to about 80 per minute, and the temperature rose to 99·5° F. Feeding became very difficult owing to the dyspnoea. Physical signs of bronchopneumonia developed on the right side of the chest, and the child died five days later.

Report of necropsy. The body was that of a poorly nourished male infant aged two months, showing some deformity of the chest, with indrawing of the lower ribs. There was no rickety enlargement of the rib junctions or epiphyses.

CENTRAL NERVOUS SYSTEM presented no abnormality visible to the unaided eye.

RESPIRATORY SYSTEM. Both lungs were the seat of acute bronchitis and bronchopneumonia. Consolidation was extensively confluent in the right lung. The upper respiratory passages showed inflammatory changes. There was an early fibrinous pleurisy on the right side.

HEART was dilated on the right side.

Nothing of pathological interest was found in the other systems.

Microscopical report

SPINAL CORD. Sections from the cervical and lumbar enlargements were examined. Both showed identical changes. The number of motor nerve cells in the anterior horns of grey matter was greatly reduced. The remaining cells were much reduced in size, shrunken and altered in shape. The Nissl substance was decreased in amount and, in many cells, present only at the periphery. Many of the nuclei were pyknotic (fig. 1). A few of the nerve cells showed satellitosis, being surrounded by a group of small cells derived from oligodendroglia or microglia. This indicated a progressive degenerative process in the cells concerned, and proved that the changes were not the result

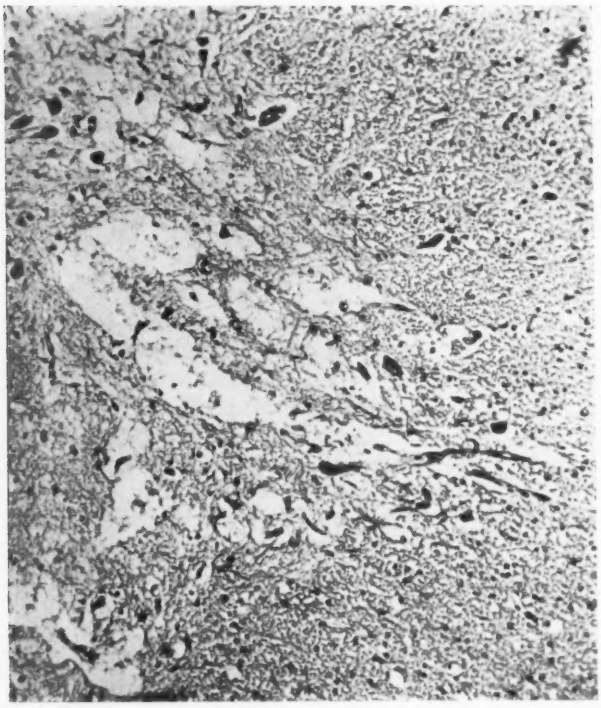

FIG. 1.—Case 1. Cervical cord, anterior horn, showing decreased number and shrunken pyknotic condition of motor nerve cells. H+E; ×100.

of post-mortem autolysis. Sections stained by selective methods for the various tissue elements of the central nervous system were not available in this case, but there appeared to be a slight increase of glia fibres in the affected parts. There was no perivascular infiltration, hyperaemia, or other evidence of inflammation.

BRAIN. In sections from the medulla oblongata, midbrain and cerebral cortex, no pathological changes were found.

Microscopical examination of the muscular tissues was not carried out.

Case 2. J. C. Admitted aged four weeks.

HISTORY. Complaint of weakness since birth and of 'turns' on several occasions. After birth it was noticed that the baby's arms were weak and that movements were limited to slight flexion at the elbows. The wrists were dropped. Legs were weak, but this was less obvious. From birth 'he has breathed with his stomach.' However, the family doctor states that flaccidity of limbs and head was noticeable at birth, but the respiratory difficulty was not so noticeable for some days. On one occasion nurse laid the baby on its abdomen, and respiration was so curtailed that the child became cyanosed. At age of one week the child 'took a turn' when he became limp and pale. Breathing was laboured. He did not twitch or become rigid, and he recovered in a few minutes. The mother thought he was becoming stronger until four days before admission when he 'took another turn.' This was more severe and lasted half an hour. He became limp and then cyanosed.

Feeding was by breast, supplemented. There was no difficulty in sucking or swallowing, no vomiting, the bowels were regular, but motions were green for a week before admission. There had been some recent loss in weight. There was no cough.

The mother's pregnancy was normal. Labour, which occurred at full-time, lasted two days; 'never had strong pains'; the head was on the perineum for a considerable time, and child easily delivered by forceps. Birth weight 7 to 8 lb.

FAMILY HISTORY. Father and mother both 28 years of age and in good health. No other children. No miscarriages. No family history of paralysis.

Examination. Length $22\frac{1}{2}$ in. Head circumference $14\frac{1}{2}$ in. Anterior fontanelle three finger-breadths open and of normal tension. No depression or other visible evidence of cranial damage. Chest poorly developed with upper ribs drawn in at the sides, and lower ribs splayed outwards. Spine and limbs of normal proportions and no evidence of any abnormality on clinical or radiological examination.

Body and limbs markedly thin; weight $6\frac{3}{4}$ lb. Skin of normal colour and texture. No cyanosis or jaundice. Temperature 97·2° F. Pulse 130 per minute. Respiration 40 to 50 per minute.

LOCOMOTOR AND CENTRAL NERVOUS SYSTEM. Child lay in characteristic position with both arms flexed at elbows and the bilateral dropped wrists lying on chest. Knees slightly flexed. Both feet appeared to be dropped, but less obviously so than the wrists (fig. 2 and 3). All muscles poorly developed

FIG. 2.—Case 2. J. C., aged 4 weeks.

FIG. 3.—Case 2. J. C., aged 4 weeks.

and of poor tone. Flexion of elbows easily overcome. Slight voluntary movement of flexion at elbows, and a suspicion of movement at shoulders. Poor movement of fingers, but no power of extension of wrists. Slight flexion of knee, and even less power of extension. Slight movement of toes. Diaphragmatic respiration with indrawing of intercostal muscles and marked protrusion of abdomen on inspiration. Abdominal muscles thin and of poor tone. No tendon reflexes elicited. No muscular twitching or fibrillation visible. Sensation to pin-prick appeared intact as child cried and attempted to withdraw limb. Cry very feeble. No ptosis or strabismus. Eye movements normal. Pupils circular, average size, equal and both reacting to light. No facial weakness. Sucking and swallowing unimpaired.

Lumbar puncture gave a drop of gelatinous fluid, followed by clear fluid with a faint yellowish colour. No evidence of increase in pressure. Pathologists report: 'Fluid contained small flakes which consisted of groups or sheets of cells with round nucleus, and a fairly large body, possibly cells of endothelial type. No organism found. Culture sterile.' Biochemistry: protein 22 mgm. per cent.; chlorides 722 mgm. per cent.; sugar 81 mgm. per cent.

Clinical examination of the other systems failed to reveal any abnormality. X-ray of chest: 'abnormal contour right cardiac border; ?congenital heart lesion.' Haemoglobin 87 per cent.; white blood cells 14,800 per c.mm.

PROGRESS. Child's condition remained stationary for several days, but then feeding became difficult and progressive weakness terminated in death one week after admission. Temperature in ward 97·8° to 98·6° F.

Report of necropsy. The body was that of a poorly nourished male infant, aged five weeks, showing deformity of chest, with forward projection of the sternum and indrawing of the ribs at the sides. The abdomen was distended and the anterior abdominal wall was very thin.

CENTRAL NERVOUS SYSTEM. Brain and spinal cord presented no abnormality visible to the unaided eye.

RESPIRATORY SYSTEM. There was extensive atelectasis of the lungs, especially the right, a large part of which was not aerated. There was no pneumonia. The upper respiratory passages were healthy.

HEART was a little dilated on the right side.

Nothing of pathological interest was found in the other internal organs.

Microscopical report

SPINAL CORD. Sections from various levels showed the same changes as those found in case 1. There was a similar reduction in the number and size of the motor nerve cells in the anterior horns, with the same changes in the structure of the cells (fig. 4). Here again a few of the cells showed satellitosis

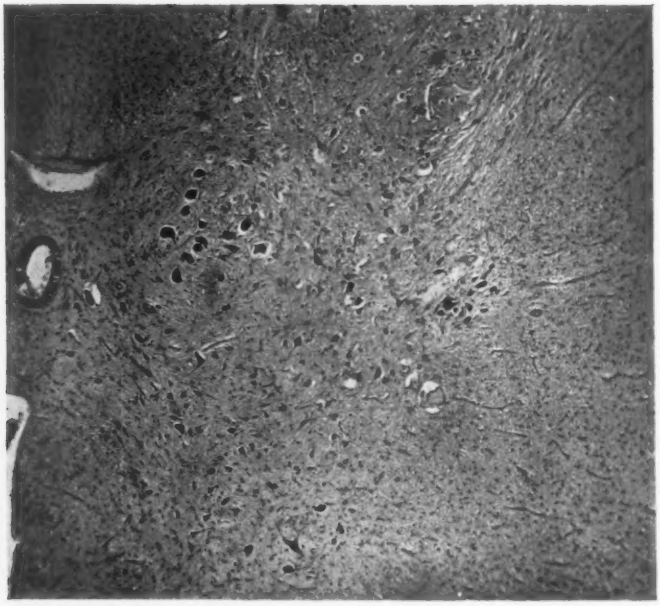

FIG. 4.—Case 2. Dorsal cord, showing anterior and posterior horns; decreased number and size of anterior horn cells; posterior horn cells unaffected. Iron haematoxylin; ×50.

(fig. 5). Sections stained by Anderson's Victoria blue method for neurolgia fibres showed a slight but definite gliosis in the region of the anterior horns, with increase of both fibres and nuclei. Sections stained with Scharlach R. revealed no fat in stainable form, indicating that no rapid degeneration of myelin was in progress. Sections of the cauda equina stained by Spielmeyer's method for myelin sheaths showed pronounced pallor of the anterior nerve roots, indicating a great scarcity of myelinated fibres there, while the posterior nerve roots were well myelinated (fig. 6).

BRAIN. Sections from the medulla oblongata, pons, midbrain, and various parts of the cerebrum showed no pathological changes.

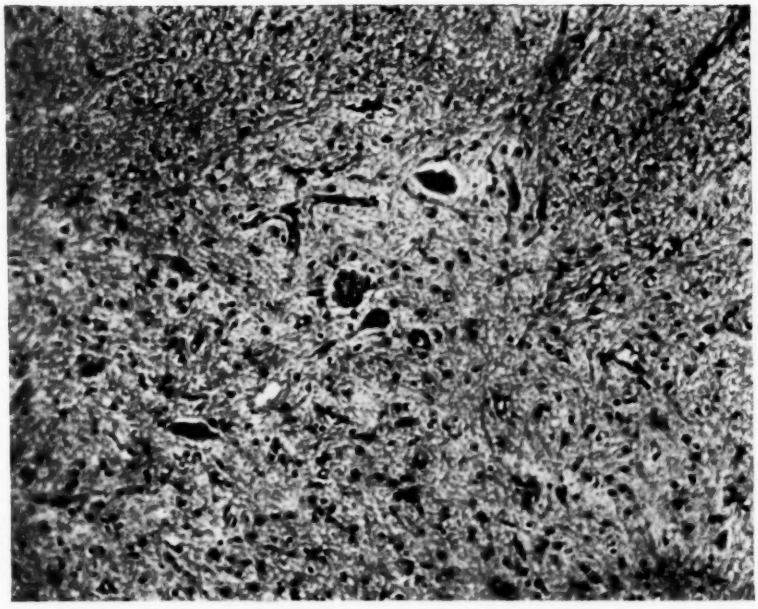

FIG. 5.—Case 2. Anterior horn, showing reduction of number of motor nerve cells, and degeneration of remaining cells. One cell in centre of field shows satellitosis.

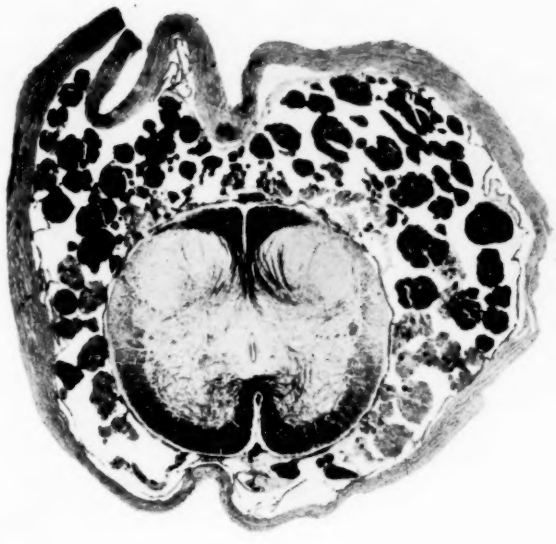

FIG. 6.—Case 2. Cauda equina showing degeneration of anterior nerve roots. Weigert Pal; ×10.

MUSCLES. Sections from heart muscle, urinary bladder, and a selection of voluntary muscles were examined. The heart and urinary bladder showed

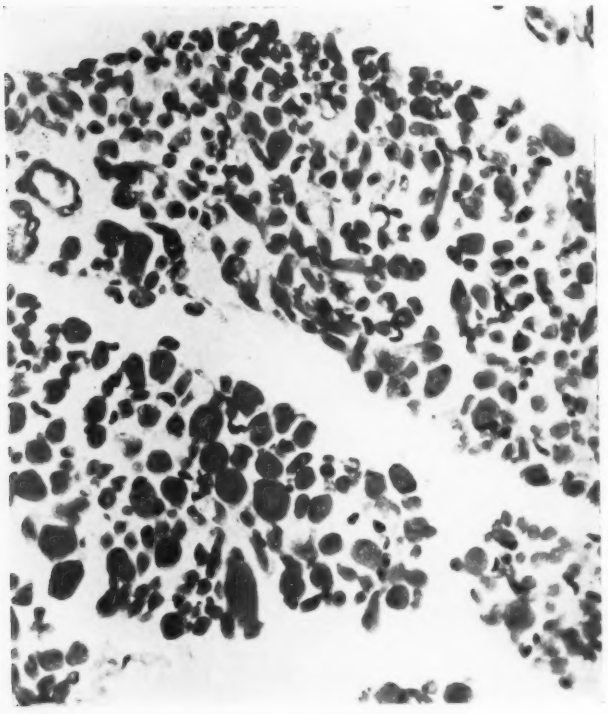

FIG. 7.—Case 2. Psoas muscle, showing detail of changes in muscle fibres. H+E; ×400.

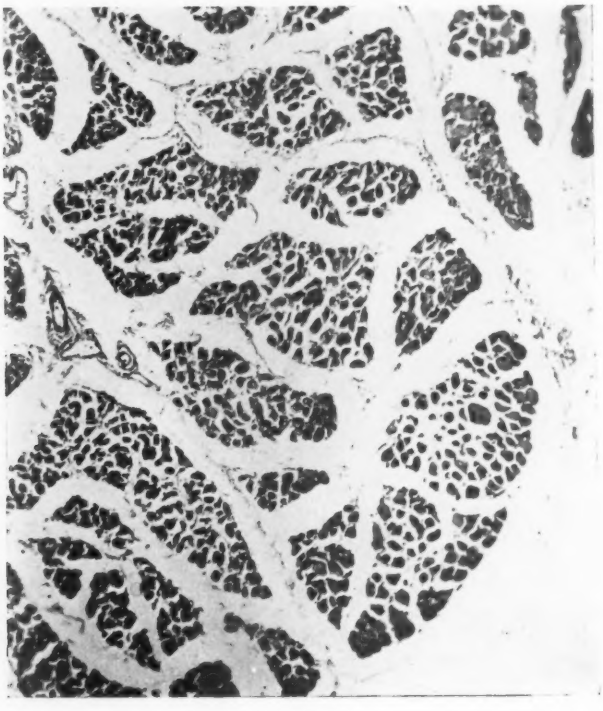

FIG. 8.—Case 2. Diaphragm, showing atrophy of muscle fibres, with irregularity of size. H+E; ×80.

nothing abnormal. The voluntary muscles all showed pathological changes. Many of the muscle fibres were greatly atrophied. The atrophy was variable, so there was a striking irregularity in the size of the fibres, even within a single bundle, some being of almost normal size whilst others were reduced to mere threads (fig. 7). Some of the most atrophied fibres were fragmented. Cross-striation was retained in the larger fibres, but could not be detected in many of the smaller. No change resembling Zenker's necrosis was observed. The fibrous stroma of the muscles was not increased. In the case of the diaphragm, the whole thickness of the muscle was much decreased, in comparison with that of a normal infant of the same age, and the same atrophy of fibres, with irregularity of size, was found as in the other skeletal muscles (fig. 8).

Discussion

The findings in both cases are in keeping with those outlined above as typical of infantile muscular atrophy of spinal origin. Vitamin E was not given a trial in either case. The atrophic changes noted in the diaphragm in case 2 have not previously been described in any recorded case that has come under our notice. Several authors, including Greenfield and Stern (1927), and Paterson (1928), have stated that the diaphragm is constantly spared. There is no obvious reason why this should be so, and it is all the more remarkable when, as was pointed out by Greenfield and Stern (1927), the frequency of severe involvement of the muscles of the neck at an early stage is considered. The evidence, however, in support of the diaphragm being unaffected is inadequate, as histological confirmation was obtained in only a minority of cases. Greenfield and Stern (1927) describe four cases of their own in two of which the diaphragm was examined histologically. The fibres were described as being small (15μ to 20μ in diameter), but as being uniform in size and shape. These changes were regarded as being normal for this muscle, and the authors conclude that 'the diaphragm . . . in all cases appeared normal.' Paterson (1928) records histological confirmation of a normal diaphragm in only one of the six cases described. He concludes, apparently mainly from clinical evidence, that, 'the intercostal and abdominal muscles are frequently affected, whereas the diaphragm remains unaffected.'

In case 2 respiration was undoubtedly diaphragmatic, and the explanation of this is probably that the changes in the intercostal muscles were in advance of those in the diaphragm. Definite atrophic changes may therefore be present in the diaphragm even if clinically it appears unaffected and indeed over-acting.

Summary

The generally accepted conception of muscular atrophy in infants is outlined.

The comprehensive term infantile muscular atrophy of spinal origin is used rather than the terms Werdnig-Hoffmann's disease and Oppenheim's disease. Reasons for this choice are given.

The outstanding features of this disease are outlined.

The possibility that some cases may prove to be muscular dystrophy is mentioned.

Attention is drawn to recent work with vitamin E, and to the possible importance of this vitamin etiologically and therapeutically in cases of infantile muscular atrophy of spinal origin.

Two new cases are described in detail and are discussed briefly, attention being drawn to the atrophic changes found in the diaphragm in one of these cases, a feature not previously recorded in the literature.

Thanks are due to Professor C. McNeil, and to the late Dr. J. McNair Murray for permission to publish these cases, and also to Dr. William Blackwood for two of the photomicrographs, to Dr. John Thomson for the photographs of the second case, and to Dr. J. L. Henderson for much helpful criticism. Dr. Agnes R. Macgregor kindly supplied all the pathological reports, and gave great help throughout.

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GROWTH OF THE LUNG IN HEALTHY AND SICK INFANTS

BY

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As correct data on the growth of the lung in infancy are not available, determination of pathological peculiarities of the infant's lung lacks a solid basis. Investigations by Aeby (1880) and a recent publication by Copoletto and Wolbach (1933) do not deal with the live volume of the lung. Aeby determined the volume of the collapsed lung in a few cases. Copoletto and Wolbach gave a statistical survey of the weight of the lungs. The growth of this organ cannot, however, be deduced from the weight; this will become apparent below in the section dealing with the specific weight. In 1935 I published a few observations on lungs which had been fixed by intravenous injection of formalin, the first observations to show the actual volume of the infant's lung. This series of figures indicates roughly the mode of growth (table 1).

TABLE 1

AGE (MONTHS)	VOLUME (C.C.)	
	RIGHT	LEFT
1	62	48
2	53	45
4	60	45
8	112	79
18	250	210

Anatomical investigations

The present investigations have been carried out in order to determine the actual volume of the expanded lung. This was intended to form the basis for investigations on the structure of the growing lung.

Method. The lungs were inflated under constant and controlled pressure. Compressed air (with the help of a water jet pump) was introduced into a flask closed by a thrice perforated rubber stopper: two of the perforations were for the entry and exit of the air, and the third was connected to a U-shaped

water manometer. Increased pressure had to be applied during the first inflation owing to the internal cohesion of the collapsed bronchioli and air-spaces. In subsequent inflations a much lower pressure proved effective. Pressure of 12–15 c.c. water, corresponding to the intrapleural (negative) pressure, restored the size and shape of the lung satisfactorily. Farber and Wilson (1933) obtained analogous results when determining the negative pressure necessary to expand the atelectatic lungs of newborn infants, using a Drinker respirator.

The lungs were allowed to remain under pressure until they were dry, and then placed in a 37° C. incubator where their weight became constant within a couple of days. The volume of the dried lung was determined by displacement.

TABLE 2

ACTUAL VOLUME OF THE RIGHT LUNG

INFANT				LUNG					
NO.	AGE (MONTHS)	WEIGHT (GRAMMES)	HEIGHT (CM.)	VOLUME (C.C.)	WEIGHT (GM.)		DRIED SUBSTANCE (PER CENT.)	VOLUME PER GM.	
					FRESH	DRIED		FRESH (C.C.)	DRIED (C.C.)
1	2	2000	48	57	33	6·7	20·3	1·8	8·5
2	0	2300	48	75	32	6·0	19·0	2·4	12·5
3	2	3100	53	77	40	8·3	20·7	1·9	9·0
4	1	2350	50	88	30	5·8	19·7	2·9	15·2
5	3	3300	54	97	31	6·5	20·8	3·0	15·0
6	4	3650	58	100	33	7·2	22·1	3·1	14·0
7	4	3700	58	110	45	9·0	20·0	2·4	12·0
8	5	3700	58	120	49	9·3	19·0	2·4	13·0
9	11	4200	61	145	86	14·7	17·0	1·7	10·0
10	7	7100	68	185	56	11·9	21·0	3·3	15·0
11	12	9300	73	200	74	15·2	20·5	2·7	13·0
12	7	6000	73	230	62	15·8	25·5	3·9	14·5
13	11	9200	73	310	92	18·6	20·2	3·4	17·0

Discussion. The lung inflated by pressure equivalent to the intrapleural pressure corresponds satisfactorily to the actual size of the breathing lung and thus affords the nearest estimate to the amount of functional lung tissue. The results are collected in table 2 and in the curve II of fig. 1. The diagram shows the volume almost continuously increasing. There is, however, something unusual in the shape of the curve. It rises slowly during the first few months and then ascends steeply; in other words, the growth of the lung, in my cases is very slow in the first few months and proceeds rapidly in the second half of the first year.

This result contrasts with the general rule of growth in infancy, i.e. the growth of the body proceeds rapidly in the first few months, far more rapidly than at any other age. Slow growth of so vital an organ as the lung and a rapidly developing body with its increased need of oxygen appear to be incompatible from a morphological as well as from a functional point of view. Further investigations appeared necessary.

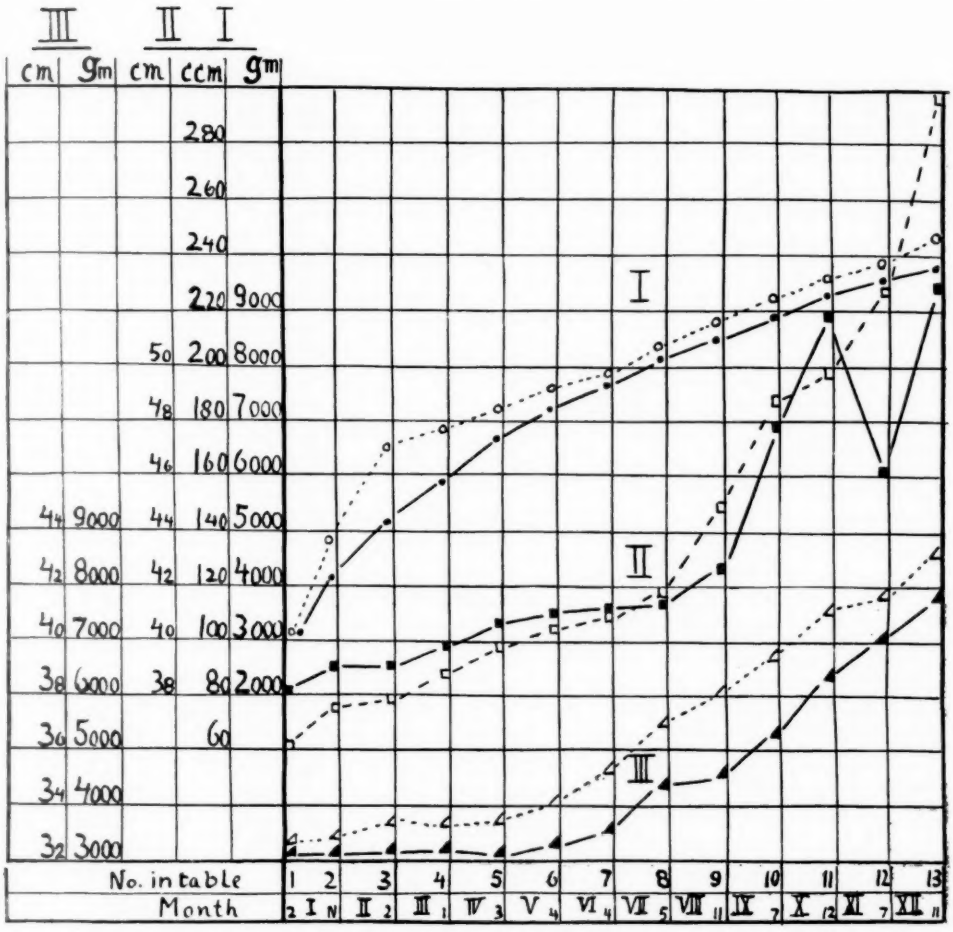

FIG. 1.—To show in I and III body-weight and circumference of the chest (after Zeltner). Curve I is that of a normal infant, curve III that of an infant which suffered from pyloric stenosis and recovered. Curve II shows the body-weight and the actual volume of the lung of anatomical cases.

The figures at the bottom of the diagram correspond in the first row to the cases in table 2. In the second row are the months, in their natural order, indicated by Latin numerals and the actual age of the cases of table 2 by small Arabic numerals.

———— = body weight in I, II, III
– – – – – – = lung volume in II
..... = circumference of the chest in I, III

Thorax and lung

Thorax and lung are reciprocally dependent on each other. In the growing lung, development is only possible if thoracic space is available; otherwise the lung remains under-developed. I was able to prove this directly (Engel and Grueneberg, 1940). The material was furnished by the lungs of a lethal mutation in the rat. The anomaly in question was a hereditary (recessive) hypertrophy of the thoracic cartilage. The growth of the ribs was definitely arrested by the hypertrophy of the cartilage, and the chest remained small and deformed. The lungs were small (as compared with the lungs of rats of the same litter and the same age), and their structure was as foetal as it is normally

in the lung of the newborn rat; according to the age, the lungs should have been fully developed and differentiated. Arrest of the growth and development of the lungs in rats with a narrow and fixed thorax admits of only one interpretation: the small space available in the deformed chest kept the lung in the undeveloped state characteristic of the lung of the newborn rat.

Clinical investigations. The intimate relationship between thorax and lung gives the opportunity of following clinically the development of the chest and lung in healthy as well as in sick infants. For this purpose the external measurements of the chest, particularly the circumference, are used; internal measurements, taken from skiagrams, serve the purpose still better.

Zeltner (1911), using the former method, made many observations on the circumference of the chest, and came to the following conclusion: the circumference increases normally from 38 to 46 cm. in the first three months, and from 46 to 51 cm. in the subsequent nine months. This means that more than 60 per cent. of the total growth in the first twelve months is completed within the first three months, a rate of progress which exceeds even that of body-growth (fig. 1). The growth of the chest (circumference) slows down or even comes to a standstill when the infant ceases to gain weight. Figures of the body-weight and of the circumference of the chest are almost parallel both in normal and pathological cases.

I can support and amplify these rough observations by radiological investigations. The skiagram shows not only the internal width, but also the height of the thoracic cavity. The method is superior to that already mentioned in that it gives two measurements instead of one and, moreover, is not rendered inaccurate by the soft parts covering the thorax which vary individually and cannot be calculated.

TABLE 3

AVERAGE FIGURES OF THE INTERNAL MEASUREMENTS

Months	0	3	6	12
Transverse diameter (cm.)	8·5	11·0	12·0	14·0
Height (cm.)	4·5	6·5	7·0	8·5

The increase in the transverse diameter amounts to 46 per cent. in the first three months, and to 64 per cent. in the first six months (the percentage relating to the total increase within the first twelve months). Similar conditions are seen in the increase in height (diaphragm to apex on the right side). The figures are 50 per cent. and 62 per cent. respectively.

My observations are corroborated by the figures published in two American papers, the first (Maresh and Washburn, 1938) dealing primarily with measurements of the heart in skiagrams, the second (Farell, 1930) with measurements of the chest of newborn infants.

The clinical investigations lead to the unequivocal conclusion that the chest (lung) of the normal infant grows fastest in the first three months. This is in

accordance with the general growth of the body. Impairment of the general condition as indicated by the loss of or stationary weight is intimately reflected in the growth of the chest. This follows from the clinical investigations of healthy and sick infants.

Specific weight of the lung

Specific weight is found to be an important feature of the growth of the lung which cannot be disregarded in the present considerations. Simultaneous determinations of volume, fresh and dry weight of the lung (table 2) show a definite relationship between size of the lung and specific weight. The lung tissue becomes lighter as age and size increase; in other words, small lungs are relatively heavier than larger lungs. The approximate figures in my series are 2·0 to 2·5 c.c. lung tissue per gramme fresh weight in younger, and 3·0 to 3·5 c.c. in older infants. Analogous figures are obtained in relation to dry weight. The decrease in specific weight is still more impressive in older children; I found 5·5 c.c. lung tissue (volume of right lung 453 c.c.) per gramme fresh weight in a child aged four years.

It may be emphasized that the specific weight is not primarily dependent on the age but on the size of the lungs, however parallel the increase may appear. Comparison of cases 11 and 13 is significant in this connexion. The two infants were almost identical as regards age, weight and height; the volume of the lungs, however, was different, viz. 200 and 310 c.c. respectively. The result of estimation of the specific weight is conclusive: the larger lung of case 13 was considerably lighter than the smaller of case 11. This individual example also illuminates the interrelationship between specific weight and volume more strikingly than the series of cases with all the changes due to chance (such as blood content) and technique.

Taking into account the decrease of specific weight as the volume of the lung increases, the weight must be rejected as a test for size and growth of the lung. The excellent paper of Copoletto and Wolbach with its many figures cannot, therefore, be used for the solution of the present problem.

Growth of the lung and general condition

The contrast between the anatomical and clinical findings appears inexplicable at first sight. However, the measurements of the chest in less thriving or wasting infants provide the clue to the problem. The growth of the chest and the lung depends simply on the general condition of the infant. Fig. 1 makes this plausible enough. All the specimens of my anatomical series came from infants far below standard weight, whereas the weight of the older infants approximates to the average with the sole exception of case 9. This case will be considered separately. On the other hand, the curve of my cases (II) differs entirely from that of a normal clinical case (I), but resembles closely the curve of an infant (III) which, whilst wasting during the first few months, gained weight in the subsequent period. The curves II and III have the following

points in common: poor general condition in the first few months and good progress in subsequent months; slow growth of the chest or lung at first, and good or even rapid advance later. The interrelationship of the weight on the one hand, and the lung volume or chest dimensions on the other can hardly be disputed. The conclusion is supported by the constancy of the relationship, indicated above in one striking example, in many cases.

The anatomical material of hospitals obviously affords little opportunity of corroborating directly the different mode of growth of the lung in normal and in pathological cases. Two of my anatomical cases, however, illustrate well the preponderating influence of the general condition (table 4).

TABLE 4

	CASE 9	CASE 12
Age (months)	11	7
Weight (gm.)	4200	6000
Height (cm.)	61	73
Volume, right lung (c.c.)	145	230

Case 9 was a much under-developed infant suffering from spastic diplegia, whereas the seven-months-old infant, No. 12, was taller than normal, the weight having been reduced rapidly. The relative size of the two lungs is significant: the older but undersized and emaciated infant had a small and the younger rather over-developed infant a large lung.

Further substantial support for the assumption that growth of the lung is arrested in wasting infants is provided histologically. The pulmonary structure of the newborn infant is so peculiar (observations to be published in detail later) that it can be recognized in any histological section. The acini are so small, to mention only one of the essential features, that full-length ductuli are met in any section. This characteristic picture persists for months in the lung of the wasting infant, a documentary proof of the developmental arrest.

Clinical and anatomical results point likewise to the connexion between growth of the lung and the infant's general condition.

General growth and growth of the lung

The arrest of the pulmonary growth in less thriving and in wasting infants presents a unique problem. The general body-growth is impaired in wasting infants only slightly or not at all; the lung, on the other hand is not only involved in severe cases, but impairment in its growth follows even any slight change in the general condition. I suggest the following explanation: The metabolism of the infant slows down whenever its general condition is impaired, less oxygen is required and superficial respiration results. The expansion of the chest, the stimulus to the growth of the thorax, is thus diminished and the chest ceases to grow. This again reacts upon the development of the lung because its growth depends on the space available. On the other hand, the reduced respiration may be a handicap to the restoration of normal metabolism. It is a vicious circle beginning with the metabolic disturbance which initiates or accompanies the loss of, or standstill in, weight.

The normal growth of the lung

Combined evaluation of the anatomical and clinical investigations leads to the following data on the growth of the lung in infancy. The right lung of the newborn infant has a volume of 60 to 70 c.c.; this volume is doubled in the first three to four months and quadrupled towards the end of the first twelve months. The left lung is smaller than the right lung (table 1); its volume amounts to 75 to 80 per cent. of that of the right lung. The decrease in the specific weight indicates that, apart from the growing volume, the relative amount of functional tissue increases as the age and volume increase.

Clinical importance

The relationship between wasting of the infant and its respiration has never been considered. The interest of paediatricians has been focussed on the intestinal and metabolic disturbances which are responsible for the deterioration of the general condition.

The impaired growth of the lung explains first the high incidence of collapse and pneumonia in wasting infants; and also suggests a new form of treatment. It might be possible to improve the general condition by influencing the respiration and thus breaking the vicious circle. This might be a considerable help in difficult dietary treatment. This question can, however, be settled only in the wards.

Summary

The lung of the normal infant grows fastest in the first few months. It doubles its volume in the first three to four months and quadruples it by the end of the first year.

The growth of the lung reacts in infancy to the slightest change, positive as well as negative, of the general condition, and comes to an almost complete standstill in wasting infants. This implies not only that the lung remains small, but also that the structural differentiation of the tissue is arrested at an early stage.

The arrest of growth and differentiation of the lung explains the high rate of collapse and pneumonia in wasting infants. On the other hand, recognition of the pulmonary impairment suggests that respiratory therapeutics may be an additional aid in the treatment of wasting infants.

Thanks are due to the medical committee of the Hospital for Sick Children, Great Ormond Street, who afforded the opportunity of carrying out the anatomical investigations and particularly to Dr. D. Nabarro, late Director of the Pathological Department. Thanks are also due to Dr. G. H. Newns and Dr. Ruby O. Stern for kind assistance.

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A FOURTH TYPE OF ERYTHROBLASTOSIS FOETALIS SHOWING HEPATIC CIRRHOSIS IN THE MACERATED FOETUS

A REPORT OF THREE CASES

(With coloured plate)

BY

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Three types of erythroblastosis foetalis are generally recognized, namely, anaemia haemolytica, which is the mildest form, icterus gravis, which is more serious, and hydrops foetalis, which is seldom compatible with independent life. The three cases recorded in this paper would seem to belong to a fourth type, not previously described, in which hydramnios is common and intrauterine death occurs some time before delivery. Foetuses of this type show little or no oedema, are severely macerated, and have a diffuse hepatic cirrhosis and splenomegaly; the placenta is greatly enlarged and pale pink in colour. This new type is the most severe manifestation of the disease, with the possible exception of cases of earlier intrauterine death resulting in miscarriage. Although an increased incidence of stillbirth is an acknowledged feature in sibships afflicted with erythroblastosis, the pathology of such cases has been neglected. Inaccessibility of material is the reason for this, as few workers on erythroblastosis have had the opportunity of studying cases in which intrauterine death has occurred.

During the last five years, I have observed fifty-two infants with erythroblastosis; nineteen recovered, twenty-four died and nine were stillborn. Twenty-nine of the series, who were born in a maternity hospital, were followed from birth and necropsies were performed in all the fatal cases. The relative frequency of the four types of the disease is given in table 1. Eighteen unobserved cases from the affected families are included.

TABLE 1

THE TYPE DISTRIBUTION OF SEVENTY CASES OF ERYTHROBLASTOSIS FOETALIS

TYPE	ANAEMIA HAEMOLYTICA	ICTERUS GRAVIS	HYDROPS FOETALIS	MACERATION WITH HEPATIC CIRRHOSIS
No. of cases ..	7	47	8	8

Case reports

Case 1. BABY O'M. Second pregnancy. Born 9/7/39. Non-hydropic macerated foetus.

Mother aged thirty-five years. Foetus of 7 lb. 1 oz. dead-born, at forty weeks, and severely macerated. Mother well throughout pregnancy, but had not felt life for a week before delivery when she had a heavy, sickly feeling. Wassermann reaction shortly after birth of this foetus, negative.

Necropsy. A well-developed male foetus showing advanced maceration. Head: No useful observations could be made owing to maceration. Thorax: Serous sacs contained blood-stained fluid, a normal feature in the macerated foetus. The lungs were unexpanded, with the appearance of healthy foetal lungs. The heart showed nothing of note. The thymus gland was small. Abdomen: Peritoneal sac contained blood-stained fluid. Alimentary tract showed nothing of interest.

LIVER. About average size, olive green, and showed bile-staining throughout. It was firmer and less diffluent than might have been expected in view of the advanced maceration, and slightly tough to cut.

SPLEEN. Greatly enlarged, measuring about three inches in diameter. It was soft and diffluent and extensively macerated.

PLACENTA. Weight 1 lb. 11 oz. (normal 1 lb. 5 oz.). 'Very unhealthy'—appearance not described.

Kidneys and other organs showed nothing noteworthy. Bones: Ribs and long bones showed no macroscopic changes.

Histology. Haematoxylin and eosin sections of all the tissues examined showed advanced maceration.

LIVER. All cell structure was lost, but there was obviously a great increase of intercellular fibrous tissue reminiscent of congenital syphilis. This was confirmed with Azan's connective tissue stain (fig. 1).

SPLEEN. All cell structure was lost. No pathological changes could be detected.

Other pregnancies. FIRST PREGNANCY. Infant of 5 lb. 2 oz. born alive, at thirty-eight weeks, in 1937, apparently healthy and survived.

THIRD PREGNANCY. Infant of 5 lb. 10 oz. born alive, at thirty-nine weeks, in 1941, with severe jaundice. Placenta weighed 1 lb. 3 oz., but appearance not mentioned. Liver and spleen enlarged. Numerous subcutaneous ecchymoses. Three hours after birth prothrombin index 34 per cent. and haemoglobin 43 per cent. (Sahli). Reticulocytes greatly increased. Death occurred thirty-seven hours after birth. The usual features of icterus gravis were seen at necropsy. Icteric index of post-mortem blood serum was 254. Microscopic examination of the liver showed the usual features of erythroblastosis, most of the erythropoietic foci were chiefly composed of large primitive erythroblasts. There was also some increase in the intercellular reticulum throughout the liver lobules, so that the cell columns were more separated from each other than usual. The portal tracts contained about the normal amount of fibrous tissue. There was no fibrosis in the spleen.

Case 2. BABY S. Third pregnancy. Born 14/9/41. Slightly hydropic macerated foetus.

Mother aged thirty-five years. Foetus of 5 lb. 10 oz. dead-born, at thirty-six weeks, and severely macerated. Mother had hydramnios for about the last six weeks of the pregnancy and had not felt life for the last two weeks. Wassermann reaction negative.

Necropsy. A small male foetus. Abdomen distended, but not tense. There was some oedema of face and head. Advanced maceration was present. Head: Nothing pathological recognized. Brain had undergone autolysis and

was semi-fluid. Thorax: Serous sacs contained a quantity of blood-stained fluid not notably in excess of that invariably found in the macerated foetus. The lungs showed nothing to note. The heart looked a little above the appropriate size; it was dilated and flaccid owing to maceration. Abdomen: Peritoneal sac contained a large quantity of blood-stained fluid definitely in excess of the amount usually found in a macerated foetus. The alimentary tract showed nothing of interest.

LIVER. Moderately enlarged, yellowish-brown, fairly soft to the touch, but definitely a little tough to cut. Its surface was perfectly smooth. It was much less diffluent than might have been expected from the stage of maceration that had been reached, and had kept its consistency much better than any of the other organs. Its colour was quite unlike the usual dull pink of ordinary macerated livers. The appearance suggested that there might be some fine diffuse fibrosis.

SPLEEN. Much enlarged, being nearly three inches in diameter. It had undergone autolysis and was soft and diffluent.

PLACENTA. Weighed 2 lb. 9 oz. (normal 1 lb. 5 oz.) and had a pale pink colour; no other observations recorded.

Other organs showed nothing of interest.

Histology. LIVER. Haematoxylin and eosin sections showed advanced maceration; no cell structure or nuclear staining remained. A diffuse, fairly uniform, fine intercellular fibrosis was visible and confirmed by application of Masson's connective tissue stain (fig. 2). It was a little denser in some parts than in others, but these bore no relation to zones of the hepatic lobule.

SPLEEN. Apart from autolytic changes, did not show anything of interest.

Sections of all tissues stained by Dobell's method did not reveal any spirochaetes.

Previous pregnancies. FIRST PREGNANCY. Infant of 8 lb. 8 oz. born alive, at forty weeks, in 1933, apparently healthy and survived.

SECOND PREGNANCY. Infant of 8 lb. 3 oz. born alive, at forty weeks, in 1938, with severe jaundice. Placenta weighed 1 lb. 10 oz.; appearance not mentioned. Liver and spleen enlarged. Haemoglobin 84 per cent. (Sahli), reticulocytes 35 per cent. and many nucleated erythrocytes. Death occurred thirty-eight hours after birth. Necropsy showed the usual features of icterus gravis and the occasional one of kernikterus. Microscopic examination of the liver showed excessive erythropoiesis, many of the erythroblasts being of a primitive type. There was no fibrosis in either liver or spleen.

Case 3. BABY T. Seventh pregnancy. Born 15/9/41. Non-hydropic macerated foetus.

Mother aged twenty-eight years. Foetus of 6 lb. 2 oz. dead-born, at thirty-eight weeks, and severely macerated. Mother felt very well throughout pregnancy, but had not felt life for ten days before delivery. Some hydramnios was observed on admission four days before delivery. Wassermann and Kahn reactions were negative after provocative injection during this pregnancy. In spite of this, a course of anti-syphilitic treatment was contemplated when the result of this pregnancy became known.

Necropsy. A small male infant showing advanced maceration. Head: Nothing of interest was found. Thorax: Organs showed the usual appearance of maceration. Abdomen: Peritoneal sac contained a quantity of blood-stained fluid, a common feature in the macerated foetus. The alimentary tract showed nothing to note.

LIVER. A little enlarged. It was light brown in colour with a greenish-yellow tinge suggesting jaundice. It was not hard but seemed slightly tough to cut. Autolysis associated with maceration had not caused it to disintegrate

as much as might have been expected and it was not diffluent. It was quite smooth on the outer surface.

SPLEEN. Enlarged to about two inches in length. It was soft but not diffluent.

PLACENTA. Weight 2 lb. 15 oz. (normal 1 lb. 5 oz.). It was very thick and had a pale pink colour.

Other organs showed nothing noteworthy.

Histology. LIVER. Cell structure destroyed by maceration. No nuclear staining. A diffuse, fine, intercellular fibrosis was shown to be fairly uniform and abundant with Masson's stain (fig. 3). Haemopoietic foci not recognizable. Sections of liver and spleen stained by Dobell's method showed no spirochaetes.

SPLEEN. Cell types not recognizable although a certain amount of nuclear staining retained. No fibrosis.

PLACENTA. Villi thickened; relatively narrow intervillous spaces. The most striking feature was an abnormal persistence of Langhans' layer of cells. The overlying syncytial cells were unusually large and numerous, frequently forming nests. No erythropoietic foci were observed, but numerous erythroblasts were seen in the vessels. The stroma was oedematous and many of the stromal cells, which were increased in number, showed enlarged, palely staining nuclei.

SUPRARENALS: A few foci of erythroblasts in the medulla.

Previous pregnancies. FIRST PREGNANCY. Infant of 8 lb. born alive, at forty weeks, in 1933, apparently healthy and survived.

SECOND PREGNANCY. Infant of 9½ lb. born alive, at forty weeks, in 1935, apparently healthy and survived.

THIRD PREGNANCY. Infant of 6½ lb. born alive, at forty weeks, in 1936, became ' extremely bloodless ' and died aged three weeks. This infant probably died from erythroblastosis of the anaemia haemolytica type.

FOURTH PREGNANCY. Infant of 6½ lb. born alive, at forty weeks, in 1938, and died aged two days. No evidence obtainable, but may well have died from erythroblastosis.

FIFTH PREGNANCY. Foetus of unknown weight stillborn, at thirty-two weeks, in 1939, when mother suffered an antepartum haemorrhage. Foetus appeared normal, but may have been affected with erythroblastosis.

SIXTH PREGNANCY. Foetus of unknown weight dead-born, at forty weeks, in 1940, in a macerated condition. Attending doctor felt sure it was syphilitic owing to its appearance and that of the placenta. This can certainly be regarded as a case of erythroblastosis in view of the necropsy findings in the foetus and placenta of the following pregnancy described above.

Comment

A family history of erythroblastosis, and identical pathological features in the three cases recorded in this paper, proves beyond all reasonable doubt that they represent a type of erythroblastosis not previously described as a definite entity. The principal features have already been mentioned, but the degenerative changes in the liver in this, and in less severe forms of the disease, merit further consideration.

Degenerative changes in the parenchymal cells of the liver, sometimes amounting to actual necrosis, are a common feature in icterus gravis and hydrops foetalis. Cirrhosis, also, is common in infants with icterus gravis who succumb after a few weeks of life, but is only occasionally seen when death occurs earlier.

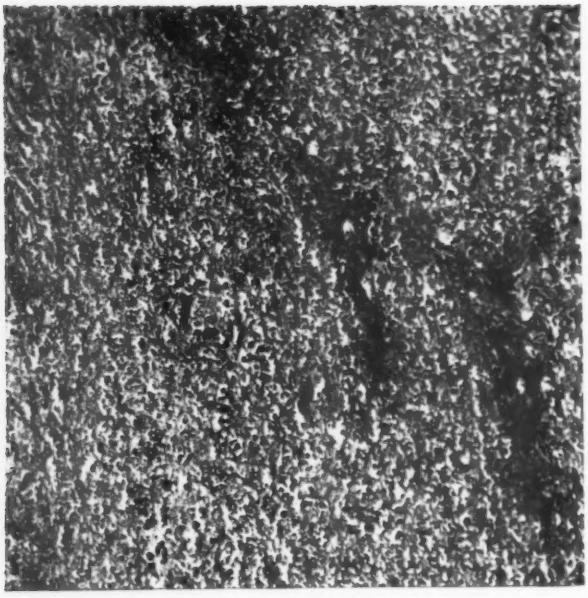

FIG. 1.—Case 1. (Liver × 75.) Azan's connective tissue stain.

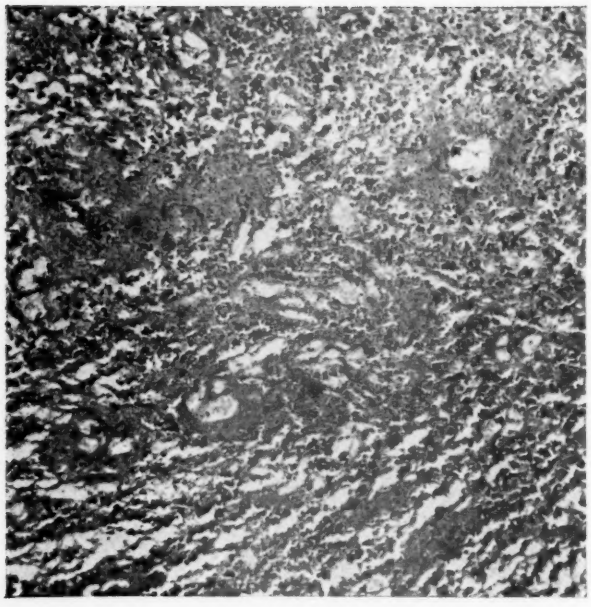

FIG. 2.—Case 2. (Liver × 55.) Masson's connective tissue stain.

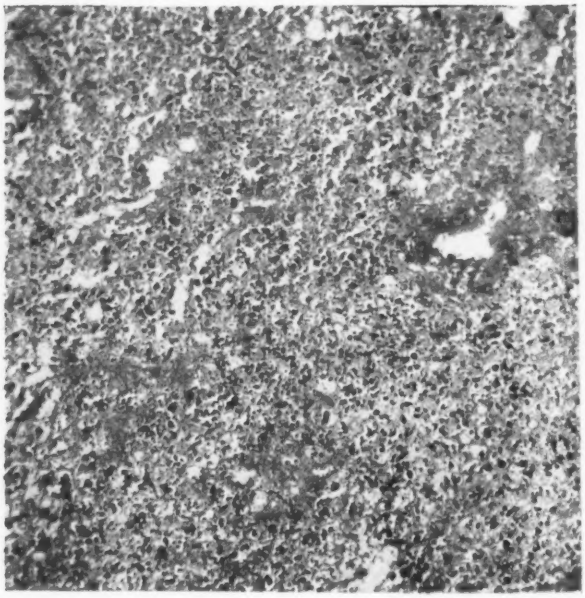

FIG. 3.—Case 3. (Liver × 55.) Masson's connective tissue stain.

Little attention had been paid to hepatic cirrhosis in erythroblastosis until its frequency was pointed out by Hawksley and Lightwood (1934). In a series of fifteen cases of icterus gravis they found hepatic cirrhosis in seven out of nine infants who had survived for longer than five weeks, but it did not occur in any of the six who died earlier. Slight degrees of cirrhosis have been recorded, however, in cases of icterus gravis in which death occurred within a few days of birth, and also in hydrops foetalis.

In the present series of thirty-three cases of erythroblastosis examined at necropsy hepatic cirrhosis was demonstrated in all three of the severely macerated foetuses, in one of the seven with hydrops foetalis and in seven of the twenty-three with icterus gravis. In the icterus gravis group, the incidence was much higher in those surviving for a few weeks. In the severely macerated foetuses, described in this paper, autolytic changes had destroyed all cell structure in the liver and the cirrhosis was of the diffuse intercellular type (fig. 1 to 3). In several of the hydrops and icterus gravis cases, severe degenerative changes, sometimes amounting to actual necrosis, were seen in the parenchymal cells of the central zone of the hepatic lobules. Fibrosis had usually begun in the necrotic areas. Two infants, who died of icterus gravis within two days of birth, showed a fine, diffuse intercellular cirrhosis, and portal cirrhosis was observed in a few cases. Occasionally, those cases showing a predominantly central or portal cirrhosis also showed a slight increase of intercellular reticulum throughout the lobule.

The pronounced degree of hepatic cirrhosis in the severely macerated foetuses, described in this paper, proves that erythroblastosis may run a long intrauterine course. This type of the disease bears a close superficial resemblance to congenital syphilis, but closer examination of the foetus and placenta renders differentiation easy. It is regrettable that such a common foetal and neonatal disease as erythroblastosis should not be generally recognized. The more severe types are still usually regarded as congenital syphilis, and the unfortunate mothers condemned as syphilitic in spite of negative serological reactions (vide case 3).

It is difficult to determine the relative frequency of this newly-described type of erythroblastosis, as affected foetuses are often not examined and therefore remain undetected. It may be more common than either hydrops foetalis or anaemia haemolytica.

Summary

Three cases of erythroblastosis in macerated foetuses are recorded.

The principal features are severe maceration, diffuse hepatic cirrhosis, splenomegaly and a large, pale pink placenta.

These cases are regarded as typical examples of a fourth clinical type of erythroblastosis which is the most severe manifestation of the disease.

Attention is drawn to the close superficial resemblance to congenital syphilis.

Thanks are due to Prof. Charles McNeil for his enthusiastic interest, and to Dr. Agnes Macgregor for the admirable pathological reports and also to Mr.

T. C. Dodds for the photographs. The Carnegie Trust for the Universities of Scotland generously helped towards the cost of the coloured illustrations.

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Addendum

Since this paper was written, another case of erythroblastosis in a macerated foetus has been observed. The features, which were identical with those in the three original cases, are recorded below.

Case 4. BABY Y. Fifth pregnancy. Born 12/12/41. Slightly hydropic macerated foetus.

Mother aged thirty-seven years. Foetus of 9 lb. 5 oz. dead-born, at thirty-eight weeks, and severely macerated. Mother felt very well until two weeks before delivery when she developed toxic symptoms. A severe degree of hydramnios developed during this time and no life was felt for ten days before delivery. Labour was induced by rupturing the membranes, when seven pints of brown-coloured liquor amnii escaped. Another two to three pints of fluid drained away after the spontaneous birth of the foetus two hours later. Wassermann reaction negative.

Necropsy. A large female foetus. A little oedema of the face and upper part of the thorax was present, but there was none in the limbs. The abdomen was enlarged, but the abdominal wall was quite lax. Advanced maceration was present. Head: Nothing pathological recognized. Thorax: Pleural sacs contained a considerable quantity of blood-stained fluid not notably in

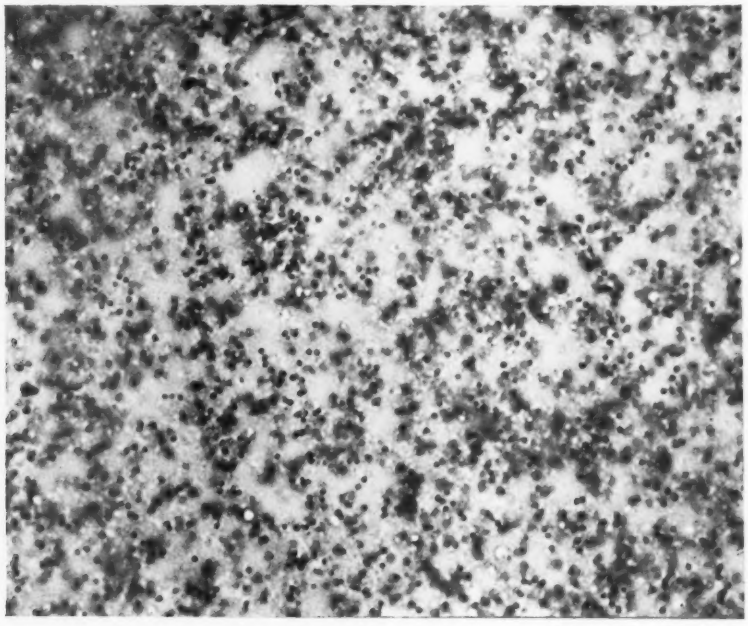

FIG. 4.—Case 4. (Blood, post-mortem, × 110.) Leishmann's stain. Erythroblasts are exceedingly numerous. In addition to the normoblasts with darkly staining, pyknotic nuclei, there are many megaloblasts with larger, palely staining nuclei.

excess of that commonly found in the macerated foetus. Pericardial sac contained only a small quantity of blood-stained fluid. Lungs showed nothing noteworthy. Heart seemed a little enlarged, but this may have been the result of relaxation of the wall owing to maceration. Abdomen: Peritoneal sac contained only a small quantity of blood-stained fluid. Alimentary tract showed nothing of interest.

LIVER. About average size, weighed 180 gm. Rather firmer than expected in view of the degree of maceration present, slightly greenish-brown and definitely, though slightly, tough to cut. There was no visible fibrosis and the outer surface was perfectly smooth.

SPLEEN. Immensely enlarged, weighed 70 gm. and measured fully 5 in. in length. Its lower pole lay to the right of the middle line and much of the abdominal enlargement was due to its great size. It was soft, lightish red and showed advanced maceration.

PLACENTA. Weight 3 lb. 15½ oz. (normal 1 lb. 5 oz.). Diameter 10 in. Thickness 1¼ in. Pale pink colour.

Other organs showed nothing of interest.

Histology. LIVER. Autolysis advanced with loss of all cell structure and nuclear staining. There was a diffuse fine fibrosis which was present everywhere, but varied a little in degree from place to place, although it had no zonal distribution. It was readily perceptible in sections stained with haematoxylin and eosin, but was shown to much greater advantage by Masson's connective tissue stain.

SPLEEN. Very little nuclear structure remained. No fibrosis.

BLOOD. A film of heart blood had resisted autolysis better than might have been expected (fig. 4). It showed a great increase in the number of nucleated red cells, including many very primitive forms.

PLACENTA. Histological characters comparable with those seen in case 3. Villi enlarged with relatively narrow intervillous spaces. The characteristic persistence of Langhans' cells could be seen here and there. The syncytial cells were increased in number, frequently forming clusters, and were often enlarged. The stroma had an oedematous appearance in some places and many of the cells, which were increased in number, showed enlarged, palely staining nuclei. No erythropoietic foci were observed, but numerous erythroblasts were seen in the vessels.

Previous pregnancies. FIRST PREGNANCY. Miscarriage.

SECOND PREGNANCY. Infant of 7 lb. born alive, at forty weeks, in 1933. Apparently healthy in infancy. Developed poliomyelitis later.

THIRD PREGNANCY. Infant of unknown weight stillborn, at forty weeks, in 1938. Anencephaly. No autopsy.

FOURTH PREGNANCY. Infant of 3 lb. 13 oz. born alive, at twenty-eight weeks, in 1940, following an antepartum haemorrhage. The placenta weighed 1 lb. 4 oz. but no further details are available. The infant died aged 11 hours. Nothing of much interest was found at autopsy. The cerebral hemispheres were excessively congested and a considerable degree of haemorrhage was seen in the posterior part of the falx cerebri. The lungs were almost completely atelectatic and sank in water. No histological examination was made.

CASE REPORT

HYDROCOLPOS IN AN INFANT

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The association of imperforate vagina with secretion and consequent retention of fluid is a rare condition in infancy. The following is a case in which it caused the death of the infant.

P. E., a female child of two months, had been noticed to have a large abdomen at birth which had become increasingly distended so that a hernia appeared at the umbilicus. The child was well fed and there was no constipation. She was the second of two illegitimate children, the elder being apparently healthy. A diagnosis of colonic dysfunction had been made and rectal catheters passed without any alteration in the size of the abdomen.

On admission the child was emaciated and restless. In the lower part of the abdomen in the mid-line there was a large cystic mass. Part of the contents of the abdominal cavity were herniated through the umbilicus, and coursing over the abdominal wall were numerous large distended veins (fig. 1). Rectal

FIG. 1.

examination revealed a large, firm, cystic swelling, situated in the mid-line, the lower pole of which was in the pelvis. X-ray showed the small bowel to be pushed into the flanks by a large opaque mass situated in the pelvis and in the middle line of the abdomen. The vulva was examined carefully, since it was thought to be oedematous, but there was no evidence of a bulging hymen. The possibility of imperforate hymen with hydrocolpos was not considered.

With increasing distension the infant began to vomit, and the general condition rapidly deteriorated. Paracentesis was performed and about 15 oz. of offensive opaque brown fluid withdrawn. The child died a few hours later. Non-haemolytic streptococci were cultured from the fluid.

Autopsy report. The body was that of an emaciated female infant with an enormously distended cystic abdomen. The parietal peritoneum was thickened and discoloured, and contained a small quantity of foul smelling fluid. The

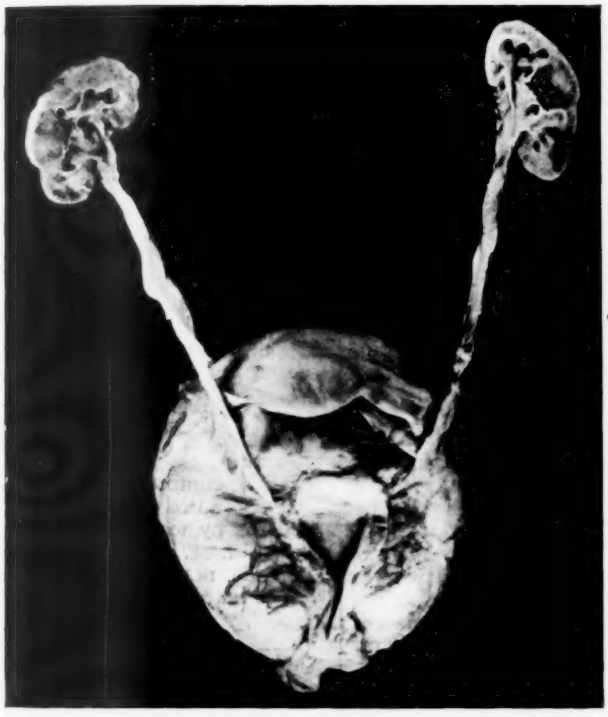

FIG. 2.

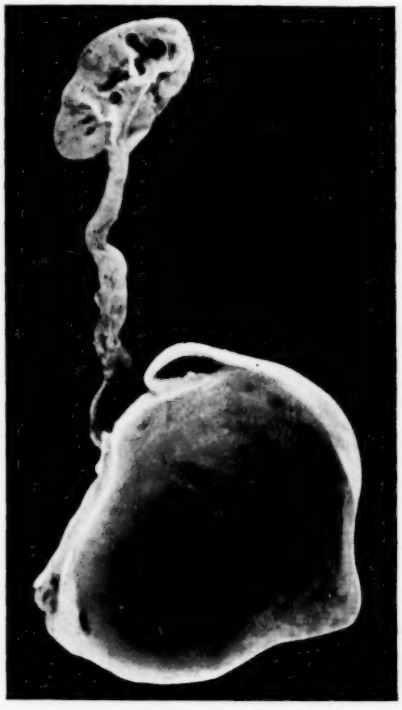

FIG. 3.

large and small intestine were compressed into a small area in the upper half of the abdomen. The mesentery of the small intestine was not attached to the posterior abdominal wall. There was a large cystic swelling arising out of the pelvis and apparently covered by peritoneum. This mass, together with the genito-urinary tract, was removed intact and dissected. It was then clear that the cyst was in continuity with the uterus which was situated at the upper pole and had been protruding through the umbilicus. The hymen was found to be imperforate, and the mass was shown to consist of the vagina, distended by fluid until it was approximately spherical and had a diameter of six inches. Both ureters were compressed with consequent dilatation and early hydronephrotic renal atrophy (fig. 2).

The mass was sectioned sagitally in the mid-line disclosing a large thick-walled cyst with no external orifice filled with 20 oz. (approximately) of dark-

brown fluid which gave a positive benzidine reaction. The wall of the cyst was smooth save at one portion, the inferior extremity, where there was a circular pigmented ulcerated area 2·0 cm. in diameter immediately in front of the anal canal. The uterus was thick-walled and of the adult type with a distended cavity (fig. 3).

TABLE

CASE NO.	AUTHOR	AGE	SIGNS AND SYMPTOMS	TREATMENT AND REMARKS
1	Breisky (1879)	Newborn	Fluctuant bleb at vulva	Incision produced abundant thick mucus, containing epithelial cells
2	Bunzel (1900)	Newborn	Tumour at vulva	Spontaneous rupture released milky fluid
3	Cranwell (1905)	1 month	Abdominal and perineal swelling	Incision produced small amount of pus with 400 g. lemon-yellow fluid. After death autopsy showed imperforate vagina with a septum a few millimetres behind the hymen. Section showed hypertrophy of vaginal and uterine epithelium.
4	Godefroy (1856)	2 months	Tumour protruding between labia	Incision produced teaspoon of mucus: hymen 2 mm. thick.
5	Guilleminet and Gayet (1938)	6 years	Abdominal pain, diarrhoea and constipation, retention of urine	Appendicectomy with later hymenotomy. Large amount of pus, varied flora. No recurrence
6	Kereszturi (1940)	6 weeks	Irritability, constipation followed 4 weeks later by anuria: tense abdominal wall, cyanotic perineum, bulging membrane between labia: pyrexia: bilateral hydronephrosis and hydroureter	Laparotomy: pelvic tumour, compression of which caused hymen to bulge; hymenotomy released 2 oz. milky fluid, sterile on culture. After 20 months hydroureter and hydronephrosis had almost recovered.
7	Melodia (1935)	7 years	Anuria for 24 hours, pelvic tumour and bulging hymen	Incision produced 300 c.c. pus with varied flora
8	Rocher and Balard (1932)	2 days	Tumour at vulva	Incision, followed by cautery and silver nitrate, produced foetid pus containing B. coli and streptococci
9	Salazar de Sousa (1934)	25 days	Loss of weight, spells of crying, vulva protruding, pyuria followed by anuria	Hymenotomy released a 'huge' (?) amount of sterile vaginal fluid
10	Wiener (1917)	12 years	Difficulty in micturition and enlarged abdomen, imperforate hymen, mass up to umbilicus	Incision produced 30 oz. of thin yellow fluid with no pus and negative culture

Comment

Ten cases (see table) have been reported in the literature occurring in female children before puberty; only three of these caused any marked symptoms, and one (case 3) caused the death of the infant. Cranwell (1905) showed that the uterine epithelium was hypertrophied in his case. It was impossible to make any histological examination owing to the unfortunate destruction of the specimen, and therefore no light can be thrown on its etiology. In spite of the rarity of the condition, it seems justifiable to draw attention to it as a cause of an abdominal swelling in infancy which may have fatal consequences, but which is amenable to simple surgical intervention.

Thanks are due to Dr. J. C. Spence for his advice and permission to publish this case.

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BRITISH PAEDIATRIC ASSOCIATION

PROCEEDINGS OF THE THIRTEENTH ANNUAL GENERAL MEETING

The Thirteenth Annual General Meeting was held at the Royal Society of Medicine, Wimpole Street, London, W.1, on Saturday, December 13, at 10 a.m.

Business Proceedings: The President, Prof. Charles McNeil (Edinburgh), was in the Chair, and there were present 22 members and 9 guests.

The Minutes of the last Meeting were read and approved.

The Treasurer's Report was received and adopted. It was decided that the usual donation of five guineas should be made to the Royal Medical Benevolent Fund and that the Treasurer be instructed to make a donation to the fund for Russian children.

After some discussion the Meeting decided that the voting for the election of Officers of the Association for 1942 should be held by post.

The Executive Committee was also instructed to discuss whether new members should be admitted and also whether women should be admitted to membership of the Association.

It was decided to leave the choice of the place and time of meeting of next year to the Executive Committee.

Scientific Proceedings:

1. DR. A. W. FRANKLIN (London): 'Giardiasis: some clinical and therapeutic observations.' He summarized the recorded facts about giardia intestinalis, stressing the high incidence of infestation in parasite surveys of children, with a peak at six years, and in dysentery convalescents. Oral atebrine (quinacrine) was a uniformly successful treatment. He described four cases with symptoms thought to be due to giardiasis: one with eleven months of diarrhoea following dysentery, two of delayed mental and physical growth with abnormal motions, and one of acute afebrile diarrhoea. Common features were the passage of bulky, undigested, mucus-containing stools of most offensive odour, abdominal distension, and partial relief on a low fat, low residue diet. Remarkable clinical improvement allowing a return to normal diet followed atebrine treatment. Giardia cysts had been found in eighteen children, six without and twelve with gastro-intestinal symptoms. Eight had been treated successfully with oral atebrine, the cysts disappearing from the stools during treatment. One adult, a never failing source of positive stools for ten years, was free of cysts from the fourth day of treatment.

The suggested doses of atebrine (quinacrine) were:—

AGE IN YEARS	DAILY DOSE IN 0·1 GM. TABLETS	COURSE IN DAYS	TOTAL DOSE
½–2	¼ × 2	3–5	0·10–0·25 gm.
2–6	½ × 2	3–5	0·30–0·50 gm.
6–9	½ × 3	4–5	0·60–0·75 gm.
9–12	1 × 2	5	1·0 gm.
Adult	1 × 3	5	1·5 gm.

The stools were examined after zinc sulphate concentration by Miss Young and Mr. Cooper in Prof. Leiper's Institute of Agricultural Parasitology at St. Albans.

2. DR. R. E. BONHAM CARTER (London) (introduced by Dr. A. G. Maitland-Jones): 'Pyuria associated with anaemia in infants.' Six cases of this association of diseases were

described. Attention was drawn to the similarity between them in history, clinical findings, and reaction to treatment. All six were under six months old, came from good homes, were under weight, had a history of loose stools, though this was not marked in hospital, a severe degree of anaemia, numerous pus cells in the urine, and grew B. coli on culture of the urine. The anaemia was such that they appeared to have less than half strength blood, with no abnormality of the red cells either in size or nucleation. Colour indices were between 0·7 and 0·85. There was a polymorphonuclear leucocytosis which corresponded with the urinary infection. Cystoscopies and retrograde pyelograms failed to demonstrate any congenital abnormality of the urinary tract. Treatment for the anaemia was divided into two periods, before and after the pyuria had been cleared up. A mixture containing 5 grains of ferrous sulphate was used during both periods in the same daily dosage for each child (10–15 grains daily according to age). The reaction to iron therapy during the first period was bad, no case having a satisfactory rise in the haemoglobin percentage. The pyuria was then successfully treated with sulphapyridine. During the second period the reaction to iron therapy was good, all the haemoglobin percentages rising satisfactorily. In the first period the reaction to blood transfusion was bad, the haemoglobin percentage falling to its original level within a week. In the second period it was better, the maximum drop in the haemoglobin percentage in the week being 16 per cent.

3. Dr. F. J. W. Miller (Newcastle-on-Tyne) (introduced by Dr. J. C. Spence): 'Analysis of 272 infant deaths.' The infant mortality in Newcastle-on-Tyne has always been above that for England and Wales. As a preliminary step in the problem, an investigation was planned, the essential feature of which was a personal inquiry by a paediatrician into the circumstances of the death of each infant occurring in 1939. The co-operation of the practitioners and the staffs of the hospitals was obtained. In this manner 272 deaths were investigated. Early in the year it was apparent that practitioners have great difficulty in the certification of death and it is estimated that one-third of the certificates gave an incorrect or inadequate description of the cause. Of the 272 deaths, 150 occurred at home and 122 in hospitals or nursing homes: 138 (50·7 per cent.) occurred within the first month and 134 in the remainder of the first year. There was a large group (41) in which no opinion of the cause of death was possible. In 54 cases the results of post-mortem examinations were available. The most important causes of death in the neonatal period were prematurity, which appeared to be the chief cause in 47 cases, birth–death (any adverse factor operative during delivery and so injuring the infant that it failed to survive) 38 cases, neonatal infection (15 cases). It is possible that the actual incidence of neonatal infection was greater than the apparent. The chief causes of death after the first month were infective conditions, which caused death in 90 out of 112 cases in which it was possible to express an opinion. These infections fell into three main groups, illnesses with respiratory symptoms, 33 cases, alimentary symptoms, 12 cases, and a large group of cases of infective origin, in which the site of infection was not localized, grouped as infections of unknown origin.

4. Dr. J. C. Spence (Newcastle-on-Tyne): 'The effects of bromides and chloral on children.' He reported on a series of observations carried out by himself and Dr. G. A. Smart in an attempt to find a suitable hypnotic for children. Bromide was first investigated, then chloral hydrate. Children between the ages of one and three were used. These children were following a daily nursery routine under which they slept in the forenoon, and played actively during the afternoon. The drug to be tested was given at noon before their mid-day meal and its effects closely observed during the remainder of the day. Potassium bromide and sodium bromide in doses up to 30 grains made none of the children sleepy. The only observable effect was to make some of them irritable and quarrelsome. Chloral hydrate in doses up to 5 grains had no effect, but 10 grains and 12½ grains brought about sleepiness. The sleep was similar to that of alcoholic intoxication, being preceded by a short period of unsteadiness and emotional change. In suitable doses chloral hydrate acted within twenty minutes, and if effects did not appear within that time did not occur later. A synergism between bromides and chloral hydrate was not definitely proved.

5. Miss E. M. Widdowson (Cambridge) (introduced by Dr. A. G. Maitland-Jones): 'The effects of wartime rationing on child health.'* Unpublished data which were obtained in a dietary survey, carried out during the years 1935–1939, on 1000 individual middle-class children have been used to determine the pre-war intakes of foods that are now rationed. A comparison of these intakes with the actual rations to-day gives a fair idea of how the present system of rationing has or has not cut across middle-class children's dietary habits. It was found that the rations provide children up to 8 years with as much meat, bacon, sugar and jam as they were having before the war. Children over 8 were formerly eating more of all these foods, and adolescent boys were eating 2 to 3 times as much as their present rations provide. The average pre-war intake of butter was more at all ages than a ration of 2 oz.

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per week, while the mean consumption of cheese was always very much less than the present weekly allowance of 3 oz.

It is suggested that, in spite of the dietary restrictions to which older children have had to submit, appetite and instinct will have led them to maintain their calories by an increased consumption of bread, potatoes and other plentiful foods. The adolescents' loss of protein, iron and vitamin B, brought about by the rationing of meat and bacon can readily be made good by an increased consumption of National Wheatmeal or wholemeal bread. So long as they receive their full domestic milk allowance, together with ½ pint of school milk a day, and if they eat their full ration of cheese, there is no reason why children's calcium intakes should fall below the corresponding pre-war figures. The calcium available for boys and girls who leave school at 14 or 15 may, however, be inadequate. If the margarine is vitaminized so that it is equal to summer butter, children up to the age of 12 can obtain more of the fat soluble vitamins from their present rations than they had from the same foods before the war. If the margarine is not vitaminized they will get less of these vitamins at all ages above one year. Vitamin C intakes have been severely curtailed as a result of the shortage of fruit. It is not known whether this is a serious matter or not.

6. Dr. J. C. Spence (Newcastle-on-Tyne) opened the discussion on 'Paediatric Policy' and dealt mainly with the establishment and the uses of paediatric departments in the teaching schools. Considering the importance of the subject and the great need for paediatric personnel for teaching, practice, public services and research, these departments as they exist at present were deplorably understaffed. The causes of this were mainly economics and apathy. The seven provincial teaching universities spend only a total of £410 a year in maintaining paediatric teaching and research. That is an average of £58 a year. In the London teaching hospitals conditions were not much better. That paediatrics had been able to survive and advance in this country in the way it had done was a tribute to the enthusiasm and good will of individual paediatricians in the face of great difficulties and handicaps. Another aspect of the economic difficulty was the poor financial return in private practice in paediatrics. It was doubtful if under present conditions the larger provincial towns could maintain more than one paediatrician, on whose shoulders so many responsibilities would rest that he would have too little time for organizing his department for teaching and for research. The solution of the problem should be sought by first establishing in the provincial teaching hospitals departments big enough to carry several people devoting themselves either wholly or partly to paediatrics. This would require a wider recognition of the importance of the subject, bigger subsidies from the universities and financial support from the local authorities for those university departments which are doing a great deal of gratuitous work for the local authorities. In setting up departments it was necessary to avoid the mistake of making a 'one-man' show. The minimum requirements would be a staff of three or four teaching physicians with three or four whole-time workers in pathology and research. There should be added to the department as members of the staff some of the child welfare or school medical officers of the local health authorities. This would inspire research work in the social factors influencing child health which had been much neglected by academic paediatricians in the past. Dealing with the London teaching schools Dr. Spence suggested that it had been a retrograde step to establish paediatric departments in each of the teaching hospitals. These tended to become one-man shows leading to competition in practice and not free from the danger of causing professional jealousy. It would have been better to group these departments in children's hospitals each serving a different area of London. It appears inevitable in the future that some better organization must be set up to establish the influence and usefulness of paediatric departments in this country, if only for the purpose of training personnel for practice and for the public services. This is a matter which must concern the Government and local authorities and therefore a great opportunity is presented to the British Paediatric Association to formulate a policy which would guide developments in the future.

Sir Wilson Jameson (Ministry of Health) said that in the past British paediatricians in this country had shown too little interest in child development and had rather confined their attention to the study of the sick child. As a result they had never assumed the responsibility which should really be theirs of advising on problems relating to the prevention of disease and the maintenance of health in children. In this they differ in no small degree from some of their colleagues in North America and particularly from those on the staff of the Toronto Children's Hospital. That hospital, which formed the Paediatric Department of the University of Toronto, provided a staff for the care of both pre-school and school children in the city of Toronto, advised both the Province of Ontario and the Dominion Government of Canada on all matters of child health, and maintained an active research department staffed mainly by wholetime workers who devoted their energies to investigations of a practical or 'applied' nature. The attitude of British paediatricians had been one rather of criticism of the work of local authorities in the field of child welfare and of the quality of the officers responsible for the performance of such work. Something more than this was needed, and, if the Association were to adopt a constructive policy such as that outlined by Dr. Spence official support for much of it would undoubtedly be forthcoming.

PROF. C. MCNEIL (Edinburgh) welcomed the remarks of Sir Wilson Jameson. It was true that the medical staffs of children's hospitals had little or no share in the preventive practice of paediatrics carried out by the child welfare clinics of the public health service ; and a closer liaison and cooperation would bring to the work of preventive paediatrics the special experience of hospital paediatricians. Dr. Spence had also stressed the importance of co-operation in any area between the hospital and child welfare departments, and had given a practical illustration of the value of such cooperation in the Newcastle investigation into the causes of infant deaths. The British Paediatric Association had now the chance of considering and framing a policy which would give its members an entry into the field of preventive medicine in infancy and childhood; and he urged that the Association should give immediate consideration to this important extension of its work.